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- (71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; 124 Grenzacherstrasse, CH-4070 Basle (CH).
- (72) Inventors: MUELLER, Werner; 10 Im Augarten, CH-4147 Aesch (CH). NEIDHART, Werner; 9, rue du Steinler, F-68220 Hagenthal le Bas (FR). PFLIEGER, Philippe; 1, rue du Vignoble, F-68130 Schwoben (FR). PLANCHER, Jean-Marc; 2, rue des Romains, F-68220 Knoeringue (FR).

- (74) Agent: WASCHBUESCH, Klaus; 124 Grenzacherstrasse, CH-4070 Basle (CH).
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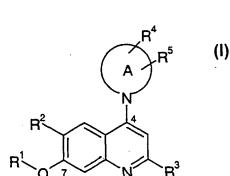
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(54) Title: QUINOLINE DERIVATIVES AS LIGANDS FOR THE NEUROPEPTIDE Y RECEPTOR

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(57) Abstract: Compounds of formula (I) as well as pharmaceutically acceptable salts and esters thereof, wherein  $R^1,\,R^2,\,R^3,\,R^4,\,R^5$  and A have the significance given in claim 1, can be used in the form of pharmaceutical preparations for the treatment or prevention of arthritis, cardiovascular diseases, diabetes, renal failure, eating disorders and obesity.

# QUINOLINE DERIVATIVES AS LIGANDS FOR THE NEUROPEPTIDE Y RECEPTOR

The present invention is concerned with novel quinoline derivatives useful as neuropeptide Y (NPY) receptor ligands, particularly neuropeptide Y (NPY) antagonists.

The invention is concerned especially with compounds of formula I

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$$R^{2}$$
 $R^{2}$ 
 $R^{3}$ 

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and pharmaceutically acceptable salts and esters thereof, wherein

R<sup>1</sup> is hydrogen, alkyl, alkoxyalkyl, alkenyl, alkinyl, hydroxyalkyl, aralkyl, heterocyclylalkyl, cycloalkylalkyl, NH<sub>2</sub>-SO<sub>2</sub>-, monoalkylamino-SO<sub>2</sub>-, dialkylamino-SO<sub>2</sub>-, alkyl-SO<sub>2</sub>-, aryl, NH<sub>2</sub>-alkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxycarbonylalkyl, carboxyalkyl, aryl-SO<sub>2</sub>-O-alkyl, cycloalkyl or cycloalkylalkyl;

R<sup>2</sup> is hydrogen, halogen, alkyl, alkenyl, alkinyl, aralkyl, heteroarylalkyl, hydroxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkoxyalkyl, aryloxy, arylamino,

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heteroarylamino, NH<sub>2</sub>-, monoalkylamino, dialkylamino, heterocyclyl, arylalkylamino, heteroarylalkylamino, aryl, arylalkoxy or heteroarylalkoxy;

R³ is hydrogen, alkyl, NH2-, monoalkylamino, dialkylamino or alkoxy;

R<sup>4</sup> is hydrogen, alkyl; cycloalkyl, alkoxy, hydroxy, NH<sub>2</sub>-, monoalkylamino, dialkylamino, acetylamino, cyano, hydroxyalkyl, alkoxyalkyl, cycloalkoxy, alkoxyalkoxy, cycloalkylalkoxy, heterocyclyl, heterocyclyloxy, heterocyclyloxyalkoxy, hydroxyalkoxy, alkoxycarbonyl, carboxy, heterocyclylalkyl, alkyl-SO<sub>2</sub>- or aryl-SO<sub>2</sub>-;

R<sup>5</sup> is hydrogen, alkyl, cycloalkyl, alkoxy, hydroxy, NH<sub>2</sub>-, monoalkylamino, dialkylamino, acetylamino, cyano, hydroxyalkyl, alkoxyalkyl, cycloalkoxy, alkoxyalkoxy, cycloalkylalkoxy, heterocyclyl, heterocyclyloxy, heterocyclyloxyalkoxy, hydroxyalkoxy, alkoxycarbonyl, carboxy, heterocyclylalkyl, alkyl-SO<sub>2</sub>- or aryl-SO<sub>2</sub>-; and armino or a solution of the second s

A is a 5- to 10- membered mono- or bicyclic saturated heterocyclic ring comprising the nitrogen atom which is attached to the quinoline ring and optionally one or two further heteroatoms which are independently selected from oxygen, sulfur and nitrogen.

The compounds of formula I and their pharmaceutically usable salts and are novel and have valuable pharmacological properties. They are neuropeptide ligands, for example neuropeptide receptor antagonists and in particular, they are selective neuropeptides Y Y5 receptor antagonists.

Neuropetide Y is a 36 amino acid peptide that is widely distributed in the central and peripheral nervous systems. This peptide mediates a number of physiological effects through its various receptor subtypes. Studies in animals have shown that neuropeptide Y is a powerful stimulus of food intake, and it has been demonstrated that activation of neuropeptide Y Y5 receptors results in hyperphagia and decreased thermogenesis.

Therefore compounds that antagonise neuropetide Y at the Y5 receptor subtype represent an approach to the treatment of eating disorders such as obesity and hyperphagia.

The current approach is aiming at medical intervention to induce weight loss or prevention of weight gain. This is achieved by interfering with appetite control, which is mediated by the Hypothalamus, an important brain region proven to control food intake. Herein, neuropeptide Y (NPY) has been proven to be one of the strongest central

mediators of food intake in several animal species. Increased NPY levels result in profound food intake. Various receptors of neuropeptide Y (NPY) have been described to play a role in appetite control and weight gain. Interference with these receptors is likely to reduce appetite and consequently weight gain. Reduction and long-term maintenance of body weight can also have beneficial consequences on con associated risk factors such as arthritis, cardiovascular diseases, diabetes and renal failure.

Accordingly, the compounds of formula I can be used in the prophylaxis or treatment of of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and obesity.

Objects of the present invention are the compounds of formula I and their aforementioned salts and esters per se and their use as therapeutically active substances; a process for the manufacture of the said compounds, intermediates, pharmaceutical compositions, medicaments containing the said compounds, their pharmaceutically usable salts and esters, the use of the said compounds, esters and salts for the prophylaxis and/or therapy of illnesses, especially in the treatment or prophylaxis of arthritis; cardiovascular diseases, diabetes, renal failure and particularly eating disorders such as hyperphagia and particularly obesity, and the use of the said compounds, salts and esters for the production of medicaments for the treatment or prophylaxis of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and obesity.

In the present description the term "alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, preferably a straight or branched-chain alkyl group with 1 to 6 carbon atoms and particularly preferred a straight or branched-chain alkyl group with 1 to 4 carbon atoms Examples of straight-chain and branched C<sub>1</sub>-C<sub>2</sub> alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, preferably methyl and ethyl and most preferred methyl.

The term "cycloalkyl" alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and preferably a cycloalkyl ring with 3 to 6 carbon atoms. Examples of C<sub>3</sub>-C<sub>8</sub> cycloalkyl are cyclopropyl, methyl-cyclopropyl, dimethylcyclopropyl, cyclobutyl, methylcyclopentyl, cyclopentyl, cyclopentyl, methylcyclopentyl, methylcyclopentyl, methylcyclopentyl, methylcyclopentyl, methylcyclopentyl, preferably cyclopropyl:

The term "alkoxy", alone or in combination, signifies a group of the formula alkyl-O- in which the term "alkyl" has the previously given significance, such as methoxy,

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ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec. butoxy and tert.butoxy, 2-hydroxyethoxy, 2-methoxyethoxypreferably methoxy and ethoxy and most preferred methoxy.

The term "aryloxy", alone or in combination, signifies a group of the formula aryl-Oin which the term "aryl" has the previously given significance, such as phenyloxy.

The term "aryl", alone or in combination, signifies a phenyl or naphthyl group, preferably a phenyl group which optionally carries one or more substituents each independently selected from halogen, trifluoromethyl, amino, alkyl, alkoxy, alkylcarbonyl, cyano, carbamoyl, alkoxycarbamoyl, methylendioxy, carboxy, alkoxycarbonyl, aminocarbonyl, alkyaminocarbonyl, dialkylaminocarbonyl, hydroxy, nitro and the like, such as phenyl, chlorophenyl, trifluoromethylphenyl, chlorofluorophenyl, aminophenyl, methylcarbonylphenyl, methoxyphenyl, methylendioxyphenyl, 1-naphthyl and 2-methylcarbonylphenyl, 3-chlorophenyl, 3-trifluoromethylphenyl, 3-aminophenyl, 4-methylcarbonylphenyl, 4-methoxyphenyl and particularly phenyl.

The term "aralkyl", alone or in combination, signifies an alkyl or cycloalkyl group as previously defined in which one hydrogen atom has been replaced by an aryl group as previously defined. Preferred are benzyl, benzyl substituted with hydroxy, alkoxy or halogen, preferably fluorine. Particularly preferred is benzyl.

The term "heterocyclyl", alone or in combination, signifies a saturated, partially unsaturated or aromatic 4- to 10-membered heterocycle which contains one or more, preferably one ore two hetero atoms selected from nitrogen, oxygen and sulfur, wherein oxygen and particularly nitrogen are preferred. If desired, it can be substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo, cyano, haloalkyl preferably trifluoromethyl and heterocyclyl, preferably morpholinyl and pyrrolidinyl, and/or on a secondary nitrogen atom (i.e. NH-) by alkyl, cycloalkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom (i.e.=N-) by oxido, with halogen, alkyl, cycloalkyl and alkoxy being preferred. The term "heterocyclyl" also includes the term heteroaryl. Examples of heterocyclyl groups are pyridinyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 3,4-dihydro-IH-isoquinolinyl, azepanyl, tetrahydrofuranyl and thiophenyl, wherein each of these rings can be substituted by one or more, preferably one or two substituents independently selected from alkyl, alkoxy, halogen, trifluoromethyl, cyano, morpholinyl and pyrrolidinyl. Particularly preferred examples of heterocycly are pyridinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiophenyl, tetrahydrofuranyl and furyl, wherein each of these rings is optionally substituted with one or more, preferably one or

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two substituents selected from alkyl, alkoxy, halogen, trifluoromethyl, cyano, morpholinyl and pyrrolidinyl.

The term "heteroaryl", alone or in combination, signifies aromatic 5- to 10-membered heterocycle which contains one or more; preferably one or two hetero atoms selected from nitrogen; oxygen; and sulfur, wherein nitrogen or oxygen are preferred. If desired, it can be substituted on one or more carbon atoms by halogen, alkyl, alkoxy, cyano, haloalkyl, heterocyclyl, preferably trifluoromethyl. Preferred heteroaryl cycles are pyridinyl or thiophenyl optionally substituted by one or more, preferably one or two substituents independently selected from halogen, alkyl, alkoxy, cyano, haloalkyl, preferably trifluoromethyl, and heterocyclyl, preferably morpholinyl or pyrrolidinyl.

The term "amino valone or in combination, signifies a primary, secondary or tertiary amino group bonded via the nitrogen atom, with the secondary amino group carrying an alkyl or cycloalkyl substituent and the tertiary amino group carrying two similar or different alkyl or cycloalkyl substituents or the two nitrogen substitutents together forming a ring, such as, for example, -NH<sub>2</sub> methylamino, ethylamino, dimethylamino, diethylamino, methyl-ethylamino, pyrrolidin-1-yl or piperidino etc., preferably amino, dimethylamino and diethylamino and particularly primary amino.

The term "halogen" signifies fluorine, chlorine, bromine or iodine and preferably fluorine, chlorine or bromine:

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The term "alkenyl", alone or in combination signifies a straight-chain or branched hydrocarbon residue comprising an olefinic bond and up to 8, preferably up to 6, particularly preferred up to 4 carbon atoms: Examples of alkenyl groups are ethenyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl and isobutenyl.

The term "alkinyl" alone or in combination signifies a straight-chain or branched hydrocarbon residue comprising a carbon carbon friple bond and up to 8, preferably up to 6, particularly preferred up to 4 carbon atoms. Examples of alkinyl groups are ethinyl, 1-propinyl, 2-propinyl, 1-butinyl, 2-butinyl and 3-butinyl.

The term "carboxy" alone or in combination signifies the -COOH group.

The term "carboxyalkyl", alone or in combination signifies an alkyl group as defined before, wherein one or more preferably one hydrogen atom is replaced by a carboxy group. An example is carboxymethyl.

The term "hydroxyalky!", alone or in combination signifies an alkyl group as define before, wherein one or more, preferably one hydrogen atom is replaced by a hydroxy group.

The term "aryloxy", alone or in combination signifies the group aryl-O-, wherein the term aryl is defined as before.

The term "cyano" alone or in combination signifies the group -CN.

The term "heterocyclyloxy", alone or in combination signifies the group heterocyclyl-O-, wherein the term heterocyclyl is defined as before.

The term "actetylamino", alone or in combination signifies the group -NH-CO-CH<sub>3</sub>.

The term "arylamino" alone or in combination signifies the group aryl-NH- or

wherein the term aryl is defined as before and, wherein both aryl groups are the same or are different.

The term "heteroarylamino", alone or in combination signifies the group heteroaryl-

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wherein the term heteroaryl is defined as before and, wherein both heteroaryl groups are the same or are different.

The term "pharmaceutically acceptable salts" refers to those salts which retain the
biological effectiveness and properties of the free bases or free acids, which are not
biologically or otherwise undesirable. The salts are formed with inorganic acids such as
hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the
like, preferably hydrochloric acid, and organic acids such as acetic acid, propionic acid,
glycolic acid, pyruvic acid, oxylic acid, maleic acid, malonic acid, succinic acid, fumaric
acid, tartaric acid, citric acid, benzoic acid, cinnamie acid, mandelic acid, methanesulfonic
acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcystein and the

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like. In addition these salts may be prepared form addition of an inorganic base or an organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts and the like. Salts derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines; substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polymine resins and the like. The compound of formula I can also be present in the form of zwitterions. Particularly preferred pharmaceutically acceptable salts of compounds of formula I are the hydrochloride salts.

The compounds of formula I can also be solvated, e.g. hydrated. The solvation can be effected in the course of the manufacturing process or can take place e.g. as a consequence of hygroscopic properties of an initially anhydrous compound of formula I (hydration). The term pharmaceutically acceptable salts also includes physiologically usable solvates.

"Pharmaceutically acceptable esters" means that compounds of general formula (I) may be derivatived at functional groups to provide derivatives which are capable of conversion back to the parent compounds in vivo. Examples of such compounds include physiologically acceptable and metabolically labile ester derivatives, such as methoxymethyl esters, methylthiomethyl esters and pivaloyloxymethyl esters. Additionally, any physiologically acceptable equivalents of the compounds of general formula (I), similar to the metabolically labile esters, which are capable of producing the parent compounds of general formula (I) in vivo, are within the scope of this invention.

The term "lipase inhibitor" refers to compounds which are capable of inhibiting the action of lipases, for example gastric and pancreatic lipases. For example or listat and lipstatin as described in U.S. Patent No. 4,598,089 are potent inhibitor of lipases. Lipstatin is a natural product of microbial origin, and or listat is the result of a hydrogenation of lipstatin. Other lipase inhibitors include a class of compound commonly referred to as panclicins. Panclicins are analogues of or listat (Mutoh et al, 1994). The term "lipase inhibitor" refers also to polymer bound lipase inhibitors for example described in International Patent Application WO99/34786 (Geltex Pharmaceuticals Inc.). These polymers are characterized in that they have been substituted with one or more groups that inhibit lipases. The term "lipase inhibitor" also comprises pharmaceutically acceptable salts of these compounds. The term "lipase inhibitor" preferably refers to or listat.

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Orlistat is a known compound useful for the control or prevention of obesity and hyperlipidemia. See, U.S. Patent No. 4,598,089, issued July 1, 1986, which also discloses processes for making orlistat and U.S. Patent No. 6,004,996, which discloses appropriate pharmaceutical compositions. Further suitable pharmaceutical compositions are described for example in International Patent Applications WO 00/09122 and WO 00/09123. Additional processes for the preparation of orlistat are disclosed in European Patent Applications Publication Nos. 185,359, 189,577, 443,449, and 524,495.

Orlistat is preferably orally administered from 60 to 720 mg per day in divided doses two to three times per day. Preferred is wherein from 180 to 360 mg, most preferably 360 mg per day of a lipase inhibitor is administered to a subject, preferably in divided doses two or, particularly, three times per day. The subject is preferably an obese or overweight human, i.e. a human with a body mass index of 25 or greater. Generally, it is preferred that the lipase inhibitor be administered within about one or two hours of ingestion of a meal containing fat. Generally, for administering a lipase inhibitor as defined above it is preferred that treatment be administered to a human who has a strong family history of obesity and has obtained a body mass index of 25 or greater.

Orlistat can be administered to humans in conventional oral compositions, such as, tablets, coated tablets, hard and soft gelatin capsules, emulsions or suspensions. Examples of carriers which can be used for tablets, coated tablets, dragées and hard gelatin capsules are lactose, other sugars and sugar alcohols like sorbitol, mannitol, maltodextrin, or other fillers; surfactants like sodium lauryle sulfate, Brij 96, or Tween 80; disintegrants like sodium starch glycolate, maize starch or derivatives thereof; polymers like povidone, crospovidone; talc; stearicacid or its salts and the like. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid-and liquid polyols and the like. Moreover, the pharmaceutical preparations can-contain preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating agents and antioxidants. They can also contain still other therapeutically valuable substances. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods known in the pharmaceutical art. Preferably, orlistat is administered according to the formulation shown in the Examples and in U.S. Patent No. 6,004,996, respectively the like s

The compounds of formula I can contain several asymmetric centers and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for

example, racemates, optically pure diastereioisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates.

In the nomenclature used in the present description the ring atoms of the quinoline ring are numbered as follows:

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Preferred are compounds of the formula I, wherein

R<sup>1</sup> is hydrogen, alkyl, alkovyalkyl, alkenyl, alkinyl, hydroxyalkyl, aralkyl, heterocyclylalkyl, cycloalkylalkyl, NH<sub>2</sub>-SO<sub>2</sub>- monoalkylamino-SO<sub>2</sub>-, dialkylamino-SO<sub>2</sub>- or alkyl-SO<sub>2</sub>-; normalisture was in the previou assemblion the ring atoms of the guinoine

R<sup>2</sup> is hydrogen, halogen, alkyl, alkenyl, alkinyl, aralkyl, heteroarylalkyl, hydroxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkoxyalkyl, aryloxy, arylamino, heteroarylamino, NH<sub>2</sub>-, mono- or dialkylamino, heterocyclyl, arylalkylamino, heteroarylalkylamino, aryl, heteroaryl, arylalkoxy or heteroarylalkoxy;

R3 is hydrogen, alkyl, NH2-, monoalkylamino, dialkylamino or alkoxy;

R<sup>4</sup> is hydrogen, alkyl, alkoxy, hydroxy, NH<sub>2</sub>-, monoalkylamino, dialkylamino, acetylamino or cyanogrounds of the translation persons

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R<sup>5</sup> is hydrogen;

A is a saturated ring consisting of a nitrogen atom which is attched to the quinoline ring and a -(CH<sub>2</sub>)<sub>n</sub>-molety with n being 4, 5, or 6;

and pharmaceutically acceptable salts and esters thereof

Preferred compounds of formula I are those, wherein R<sup>1</sup> is hydrogen, alkyl, alkenyl, hydroxyalkyl, aralkyl, heterocyclylalkyl, cycloalkylalkyl, dialkylamino-SO<sub>2</sub>-, alkyl-SO<sub>2</sub>-, dialkylaminoalkyl, alkoxycarbonylalkyl, aryl-SO<sub>2</sub>-O-alkyl or cycloalkylalkyl.

In a further preferred embodiment of the invention R<sup>1</sup> is hydrogen, alkyl, alkoxyalkyl, alkenyl, alkinyl, hydroxyalkyl, aralkyl, heterocyclylalkyl, cycloalkylalkyl, NH<sub>2</sub>-, mono- or dialkylamino-SO<sub>2</sub>-, or alkyl-SO<sub>2</sub>-. A further preferred embodiment of the present invention R<sup>1</sup> is hydrogen, cycloalkylalkyl, aralkyl, or heteroarylalkyl. Further

preferred are compounds according to formula (I), wherein R¹ is hydrogen, aralkyl or heteroarylalkyl. Particularly, preferred are compounds of formula (I), wherein R¹ is hydrogen, phenylalkyl or pyridinylalkyl wherein the phenyl- and the pyridinyl cyles are optionally substituted with one to three substituents independently selected from the group consisting of alkyl, alkoxy, cyano, or halogen, preferably, methyl, alkoxy, cyano, or halogen. Further particularly preferred are compounds, wherein R¹ is hydrogen, cyclopropylmethyl, (methoxyphenyl)methyl, (cyanophenyl)methyl, (chlorophenyl)methyl, pyridinylmethyl, (fluropyridinyl)methyl, (chloropyridinyl)methyl, or (methylpyridinyl)methyl. Very preferred are compounds, wherein R¹ is hydrogen, cyclopropylmethyl, (methoxyphenyl)methyl, (cyanophenyl)methyl, (chlorophenyl)methyl or pyridinylmethyl. Particularly preferred are compounds of formula I, wherein R¹ is hydrogen, cyclopropylmethyl, (methoxyphenyl)methyl, (cyanophenyl)methyl, (chlorophenyl)methyl, (chlorophenyl)methyl,

In a preferred emodiment of the present invention R<sup>2</sup> is hydrogen, halogen, alkyl, alkenyl, alkinyl, aralkyl, heteroarylalkyl, hydroxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkoxyalkyl, aryloxy, arylamino, heteroarylamino, NH<sub>2</sub>-, mono- or dialkylamino or aryl(alkyl)amino. In another preferred embodiment of the invention R<sup>2</sup> is hydrogen, alkyl, or halogen. Particularly preferred are compounds of formula (I), wherein R<sup>2</sup> is hydrogen. Likewise preferred are compounds according to formula (I), wherein R<sup>2</sup> is alkyl.

Other preferred compounds of formula (I) are those, wherein R<sup>2</sup> is hydrogen, butyl, fluoro or bromo. Particularly preferred are hydrogen, butyl, fluoro or bromo.

A preferred aspect of the present invention are compounds according to formula I, wherein R<sup>3</sup> is hydrogen, alkyl, aralkoxy, heteroarylalkoxy, NH<sub>2</sub>-, mono- or di-alkylamino. Further preferred compounds of formula (I) are those, wherein R<sup>3</sup> is hydrogen, alkyl, or NH<sub>2</sub>-. Preferred compounds are those, wherein R<sup>3</sup> is alkyl, particularly methyl.

Preferred are compounds of formula I, wherein R<sup>4</sup> is hydrogen, alkyl, cycloalkyl, alkoxy, hydroxy, monoalkylamino, dialkylamino, hydroxyalkyl, alkoxyalkyl, cycloalkoxy, alkoxyalkoxy, cycloalkylalkoxy, heterocyclyl, heterocyclyloxyalkoxy, hydroxyalkoxy, alkoxycarbonyl, heterocyclylalkyl or alkyl-SO<sub>2</sub>

In a preferred embodiment of the invention R<sup>4</sup> is hydrogen, alkyl or alkoxy. Another preferred aspect of the present invention are compounds of formula (I), wherein R<sup>4</sup> is hydrogen or alkoxy. Particularly preferred compounds of formula I are those, wherein R<sup>4</sup> is hydrogen, alkoxy alkoxy alkoxy alkyl; hydroxyalkyl or hydroxy. Very preferred is hydrogen.

Further preferred are those compounds of formula I, wherein A is a 5- to 10-membered mono- or bicyclic saturated heterocyclic ring comprising the nitrogen atom which is attached to the quinoline ring and optionally one or two further oxygen atoms. Preferred compounds according to formula I are those, wherein A is pyrrolidinyl, azepanyl, morpholinyl, 1,4-dioxa-8-aza-spiro(4.5)dec-8-yl or piperidinyl.

Other preferred compounds of formula (I) are those, wherein A is a pyrrolidinyl or azepanyl ring. Particularly preferred is a pyrrolidinyl ring.

Preferred compounds of formula I are those, wherein R<sup>5</sup> is hydrogen.

Examples of preferred compounds of formula (I) are

- 10 1. 7-Benzyloxy-2-methyl-4-pyrrolidin-1-yl-quinoline;
  - 2. 2-Methyl-4-pyrrolidin-1-yl-quinolin-7-ol; ionally out on further spaces at the
  - 3. Dimethyl-sulfamic acid 2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl ester;
  - 4. Methanesulfonic acid 2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl ester;
  - 5. 7-Cyclopropylmethoxy=2=methyl-4-pyrrolidin-1-yl-quinoline;
- 15 6. 7-(3-Methoxy-benzyloxy)-2-methyl-4-pytrolidin-1-yl-quinoline;
  - 7. 7-Methoxy-2-methyl-4-pyrrolidin-I-yl-quinoline;
  - 8. 2-Methyl-7-(pyridin-2-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;
  - 9. 7-Allyloxy-2-methyl-4-pyriolidin-l-yl-quinoline;
  - 10. 7-Isobutoxy-2-methyl-4-pyrrolidin-1-yl-quinoline; supposition i
- 20 11. 7-(2-Methoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
  - 12. 2-Methyl-4-pyrrolidin-1-yl-7-(tetrahydro-furan-2-ylmethoxy)-quinoline;
  - 13. 7-(4-Methoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
  - 14. 2-(2-Methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
  - 15. 4-(2-Methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
- 25 16. 2-Methyl-4-pyrrolidin-1-yl-7-(2-trifluoromethyl-benzyloxy)-quinoline;

- 17. 2-Methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethyl-benzyloxy)-quinoline;
- 18. 2-Methyl-4-pyrrolidin-1-yl-7-(4-trifluoromethyl-benzyloxy)-quinoline;
- 19. 7-(2-Chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
- 20. 7-(3-Chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
- 5 21. 7-(4-Chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
  - 22. 2-Methyl-7-(pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;
  - 23. 3-(2-Methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
  - 24. 7-Isopropoxy-2-methyl-4-pyrrolidin-1-yl-quinoline;
  - 25. 7-(2-Methoxy-ethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
- 10 26. 2-Methyl-7-(2-morpholin-4-yl-ethoxy) 4-pyrrolidin-1-yl-quinoline;
  - 27. 2-Methyl-7-(pyridin 4-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;
  - 28. (S)-'7-Benzyloxy-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinoline;
  - 29. (S)-4-(3-Ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol;
  - 30. (S)-4-(3-Ethoxy-pyrrollidin-1-yl)-7-(3-methoxy-benzyloxy)-2-methyl-quinoline;
- 15 31. (S)-4-[4-(3-Ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
  - 32. (S)-2-[4-(3-Ethoxy pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
  - 33. 7-Benzyloxy-6-butyl-4-pyrrolidin-1-yl-quinoline;
  - 34. 6-Butyl-4-pyrrolidin-1-yl-quinolin-7-ol;
  - 35. 6-Butyl-7-methoxy-4-pyrrolidin-1-yl-quinoline;
- 20 36. 6-Butyl-7-ethoxy-4-pyrrolidin-1-yl-quinoline;
  - 37. 6-Butyl-7-cyclopropylmethoxy-4-pyrrolidin-1-yl-quinoline;
  - 38. 4-(6-Butyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
  - 39. 4-Azepan-1-yl-7-berizyloxy-2-methyl-quinoline;

- 40. 4-Azepan-1-yl-2-methyl-quinolin-7-ol;
- 41. 4-Azepan-1-yl-2-methyl-7-(pyridin-4-ylmethoxy)-quinoline;
- 42. 4-(4-Azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile;
- 43. 3-(4-Azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile;
- 5 44. 4-Azepan-1-yl-2-methyl-7-(pyridin-2-ylmethoxy)-quinoline;
  - 45. 6-Bromo-7-methoxy-2-methyl-4-pyrrolidin-1-yl-quinoline;
  - 46. 6-Bromo-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol;
  - 47. 4-(6-Bromo-2-methyll-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
  - 48. 7-Methoxy-4-pyrrolidin-1-yl-quinolin-2-ylamine;
- 10 49. 7-Methoxy-4-pyrrolidin Tyl-quinoline described between the
  - 50. 4-Pyrrolidin-1-yl-quinolin-7-olpotical vlorymethyl-herses trile
  - 51. 7-(3,5-dimethoxy-benzyloxy)-2-methyl-4-pyrrolidin-T-yl-quinoline;
  - 52. 7-(3,4-dimethoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
  - 53. 7-ethoxy-2-methyl-4-pyrrolidin-1-yl-quinoline;
- 15 54. 2-Methyl-7-(6-methyl-pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;
  - 55. 2-methyl-7-(2-methyl-pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;
  - 56. 7-(6-chloro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
  - 57. 7-(2-chloro-pyridin-3-ylimethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
  - 58. 7-(2-fluoro-pyridin-3 ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
- 20 59. 7-(2-chloro-6-methyl-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
  - 60. 7-(2-chloro-6-trifluoromethyl-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
  - 61. 5-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-pyridine-2-carbonitrile;

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- 62. 7-(5-chloro-thiophen-2-ylinethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
- 63. 2-methyl-4-pyrrolidin-1-yl-7-(thiophen-3-ylmethoxy)-quinoline;
- 64. 4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-benzonitrile;

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- 65. (S) 4-(3-ethoxy-pyrrollidin-1-yl)-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methylquinoline;
  - 66. (S) 7-(2-chloro-pyridin-3-ylmethoxy)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methylquinoline;
  - 67. (S) 4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-7-(pyridin-3-ylmethoxy)-quinoline;
  - 68. (S) 5-[4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-pyridine-2-carbonitrile;

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69. 4-azepan-1-yl-7-(3-methoxy-benzyloxy)-2-methyl-quinoline;

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- 70. 2-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile;
- 71. 4-azepan-1-yl-7-(3-chloro-benzyloxy)-2-methyl-quinoline;
- 72. 4-Azepan-1-yl-7-(4-chloro-benzyloxy)-2-methyl-quinoline;

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- 73. 2-methyl-7-(6-morpholin-4-yl-pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;
  - 74. 2-methyl-4-pyrrolidin-1-yl-7-(6-pyrrolidin-1-yl-pyridin-3-ylmethoxy)-quinoline;
  - 75. [2,2-dimethyl-3-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-propyl]-dimethyl-amine;
  - 76. 2-methyl-7-(1-methyl-piperidin-4-yloxy)-4-pyrrolidin-1-yl-quinoline;
- 20 77. 2-methyl-4-pyrrolidin-1-yl-7-(tetrahydro-furan-3-yloxy)-quinoline;
  - 78. 2-Methyl-7-(1-methyl-piperidin-4-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;
  - 79. 2-methyl-7-(3-morpholin-4-yl-propoxy)-4-pyrrolidin-1-yl-quinoline;
  - 80. (2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-acetic acid ethyl ester;
  - 81. 2-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-ethanol;

- 82. toluene-4-sulfonic acid 2-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-ethyl ester;
- 83. 2-methyl-7-(3-pyridin-2-yl-propoxy)-4-pyrrolidin-1-yl-quinoline;
- 84. 7-benzyloxy-2-methyl-4-morpholin-4-yl-quinoline;
- 85. (S)-1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-3-ol;
- 5 86. (R)-1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrròlidin-3-öl;
  - 87. (S)-[1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-2-yl]-methanol;
  - 88. (S)-7-benzyloxy-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline;
  - 89. (S)-4-(2-Methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol;
- 90. (S)-7-(2-chloro-pyridin-3-ylmethoxy)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2methyl-quinoline:
  - 91. (S)-7-(2-fluoro-pyridin-3-ylmethoxy)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline;
  - 92. (S)-7-cyclopropylmethoxy-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline;

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- 93. (S)-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol;
- 94. (S)- {1-[7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-quinolin-4-yl]-pyrrolidin-2-yl}-methanol;
  - 95. (S)- {1-[7-(2-chloro-pyridin-3-ylmethoxy)-2-methyl-quinolin-4-yl]-pyrrolidin-2-yl}-methanol;
  - 96. (S)- 2-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
    - 97. (S)- {1-[2-methyl-7-(pyridin-3-ylmethoxy)-quinolin-4-yf]-pyrrolidin-2-yl}-methanol;
    - 98. (S)- 5-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl-pyridine-2-carbonitrile;
    - 99. 7-benzyloxy-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline;
- 25 100. 6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol;

- 101. 4-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
- 102. 6-fuoro-2-methyl-7-(pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline;
- 103. 6-fluoro-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
- 104. 7-(2-chloro-pyridin-3-ylmethoxy)-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline;
- 5 105. 6-fluoro-2-methyl-7-(2-methyl-pyridin-3-ylmethoxý)-4-pyrrolidin-1-yl-quinoline;
  - 106. 3-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
  - 107. 2-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
  - 108. 7-cyclopropylmethoxy-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline;

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- 109. 5-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ylokymethyl)-pyridine-2-10 carbonitrile;
  - 110. (R)-7-benzyloxy-4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinoline;
  - 111. (S)-7-benzyloxy-4-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinoline;
  - 112. (S)-7-benzyloxy-4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinoline;
  - 113. (S)-7-benzyloxy-4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-2-methyl-quinoline;
- 15 114. (S)-7-benzyloxy-4-[3-(3-methoxy-propoxy)-pyrrolidin-1-yl]-2-methyl-quinoline;
  - 115. 7-benzyloxy-2-methyl-4-{(3S)-3-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-pyrrolidin-1-yl}-quinoline;
  - 116. (S)-4-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-ol;
  - 117. (S)-4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol;
- 20 118. (S)-4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol;
  - 119. (S)-4-[3-(3-methoxy-propoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-ol;
  - 120. 2-methyl-4-{(3S)-3-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-pyrrolidin-1-yl}-quinolin-7-ol;

121. (S)- 4-{4-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-yloxymethyl}-benzonitrile;

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- 122. (S)- 4-[4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
- 5 123. (S)-4-[4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitřile;
  - 124. (S)-4-{4-[3-(3-methoxy-propoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-yloxymethyl}-benzonitrile;
- 125. (S)-4-{4-[3-(2-Hydroxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-yloxymethyl}-benzonifrile;

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126. (S)-[1-(7-benzyloxy-6-fluoro-2-methyl-quinolin-4-yl)-pyrrolidin-2-yl]-methanol;

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- 127. (S)-6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol;
- 128. (S)-4-[6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
- 15 129. (S)-5-[6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-pyridine-2-carbonitrile;
  - 130. (S)-4-[4-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
- - 132. (R,S)-4-[2-methyl-4 (2-methyl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]benzonitrile;
  - 133. (S)-4-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
- 25 134. (R)-4-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

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135. (R)-4-[4-(3-dimethylamino-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;

- 136. (S)-4-[4-(3-dimethylamino-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
- 137. (R)-4-[4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
- benzonitrile;
  - 139. (R,S)-4-[4-(2-isopropyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
- 140. (S)-1-[7-(4-cyano-benzyloxy)-2-methyl-quinolin-4-yl]-pyrrolidine-2-carboxylic acid methyl ester;
  - 141. (R)- 4-[2-methyl-4-(3-methylamino-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile;
  - 142. (S)- 4-[2-methyl-4-(3-methylamino-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile;
- 15 143. 4-(2-methyl-4-piperidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;

- 144. 4-(2-methyl-4-morpholin-4-yl-quinolin-7-yloxymethyl)-benzonitrile;
- 145. (R,S)-4-[4-(3-diethylamino-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
- 146. (R,S)-4-[2-methyl-4-(3-pyridin-2-yl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]20 benzonitrile;
  - 147. (R,S)-4-[2-methyl-4-(3-pyridin-4-yl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile;
  - 148. (S)- 4-[2-methyl-4-(2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile;
- 25 149. (R,S)-4-[4-(3-methanesulfonyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]benzonitrile;
  - 150. (R,S)-4-[2-methyl-4-(3-methyl-piperidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile;

- 151. 4-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile and
- 152. (R,S)- 4-[4-(3-hydroxymethyl-piperidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile.

Examples of particularly preferred compounds of formula (I) are

- 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol;
- 7-(3-methoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

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- 2-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
- 10 4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
  - 7-(3-chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
  - 7-(4-chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
  - (S)-4-[4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
  - 6-butyl-4-pyrrolidin-1-yl-quinolin-7-ol;
- 15 4-(6-butyl-4-pyrrolidin 1-yl-quinolin-7-yloxymethyl)-benzonitrile;
  - 4-azepan-1-yl-2-methyl-7-(pyridin-4-ylmethoxy)-quinoline;
  - 4-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile;
  - 3-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile;
  - 7-(2-chloro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
- 20 (S) 4-(3-ethoxy-pyrrolidin-1-yl)-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-quinoline;
  - (S) 7-(2-chloro-pyridin-3-ylimethoxy)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinoline;
  - (S)-7-(2-chloro-pyridin-3-ylmethoxy)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline;

- (S)-7-(2-fluoro-pyridin-3-ylmethoxy)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline;
- (S)-{1-[7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-quinolin-4-yl]-pyrrolidin-2-yl}-methanol;
- 5 (S)- {1-[7-(2-chloro-pyridin-3-ylmethoxy)-2-methyl-quinolin-4-yl]-pyrrolidin-2-yl}-methanol;
  - 4-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxýmethyl)-benzonitrile; 6-fluoro-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
  - 7-(2-chloro-pyridin-3-ylimethoxy)-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline;
- 10 (S)-4-[4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
  - (S)-4-[6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
  - (S)-4-[4-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
  - (R)-4-[4-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
- 15 (S)-4-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile and
  - (R)-4-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile.

Processes for the manufacture of compounds of formula I are an object of the invention.

The substituents and indices used in the following description of the processes have the significance given above unless indicated to the contrary.

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Compounds of general formula I can be obtained according to scheme 1 from compounds of formula Ia comprising R<sup>2</sup> substituents according to the above definition by an alkylation reaction with, e.g. K<sub>2</sub>CO<sub>3</sub> as a base and in a suited solvent such as DMF. The alkylation reaction to introduce R<sup>1</sup> can also be performed on the intermediates described below, prior to implementation of the substituents in 4-quinoline pointion by inverting the reaction steps.

Alternatively, compounds of formula I can be obtained from Ib, according to scheme 2, by an alkylation reaction as above to give compounds of formula 1c and subsequent Pd catalysed C/O, C/N or C/C bond forming reactions in analogy to known procedures. Thus, substituted alkoxy, and amino groups can be introduced via a C/O, C/N bond forming reaction under Buchwald conditions, from the corresponding alkohols and amines with, for example, Pd(OAc)<sub>2</sub> as catalyst, BINAP (2,2-bis(dipenylphosphino)-1,1-binaphthyl) as chelating phosphine ligand and with NaOtBu as a base - in a solvent such as toluene and at elevated temperature (S. L. Buchwald in: J Am. Chem. Soc. 1996, p. 10333 and Acc. Chem Res. 1998, p 805 for the general method).

With repect to Pd catalysed C/C bond forming methods to introduce the above defined substituted alkyl and (hetero)aryl groups: This can be achieved via Suzuki-type coupling (for aryl, heteroaryl substitutents) starting from well described or commercial aryl or heteroaryl boronic acids with, for example, Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst, Na<sub>2</sub>CO<sub>3</sub> as base, in DMF at elevated temperature (general method: Synth. Commun. 1991, p 513). An alternative consists in using the corresponding aryl or heteroaryl stannanes in a Stille-type coupling (for general method: Ang. Chem IE, 1986, 508).

Procedures to introduce arylalky, heteroarylalkyl consists of applying the reaction discussed above or to use Pd catalysed C/C bond formation under Negishi conditions, starting from the known arylalkyl; heteroarylalkyl Li or Mg salts, with Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst, in the presence of ZnCl<sub>2</sub> and in THF as solvent (general method: Acc. Chem. Res. 1982, p340). Other methods (e.g for arylethyl, heteroarylethyl group introduction) consists of performing a Heck-type coupling, starting from a corresponding (hetero)aryl olefine and 1c, with Pd<sub>2</sub>(dba)<sub>3</sub> as catalyst, P(t-Bu)<sub>3</sub> as phosphine ligand, CsCO<sub>3</sub> as base in DMF as

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solvent at elevated temperature. (G.C. Fu'in: J. Orgo Chem. 1999, p. 10 for recent application of the reaction). The (hetero) available condensation products can then be reduced further by hydrogenation.

A method to introduce alkinyl groups consists of reacting an alkine with 1c under the Sonogashira conditions (review: Org. Prep. Proceed: Int. 1995, p127) with Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst, in the presence of CuI and with triethyl amine as a base. Alkenyl dervivatives are obtained from alkenes via Heck coupling as pointed out above, and alkyl as R<sup>2</sup> substituent can be obtained from the corresponding alkenes by hydrogenation.

An alternative sequence to perform above discussed Stille-, Negishi and Suzuki-type condensations consisits of performing an halogen/metal exchange reaction from Ic, to obtain the corresponding standanes, Li or Mg salts or boronic acids. This is then followed by a Pd-catalysed condensation with appropriate halogenides (R<sup>2</sup>Hal) according to the general methods given above.

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$$\begin{array}{c}
A \\
N \\
R \\
O \\
N \\
R^3
\end{array}$$

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R<sup>2</sup> is halogen, alkyl, alkenyl, alkinyl, aralkyl, heteroarylalkyl, hydroxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkoxyalkyl, aryloxy, arylamino, heteroarylamino, NH<sub>2</sub>-,

mono- or dialkylamino, heterocyclyl, arylalkylamino, heteroarylalkylamino, aryl, heteroaryl, arylalkoxy or heteroarylalkoxy.

Compounds of general formula I can also be prepared according to scheme 3 from compounds of formula II with appropriate alkohols (R<sup>1</sup>OH) in a Pd catalysed C/O bond forming reaction under Buchwald conditions as discussed above or by Ullman-type rection with, for example CuCl, in a solvent such as DMF, in analogy to a method described by J.A. Ragan: Synthesis 1998, p1599.

## Compounds of general formula Ia, b and II can be prepared as follows:

The preparation of compounds according to formula Ia1, wherein R³ is not-NH2-, alkylamino, dialkylamino of alkoxy, is achieved is according to scheme 4, starting from appropriate anilines which are either known in the literature or which can being prepared by standard procedures known in the art. Thus, condensation with corresponding alkoxycarbonyl ketones or aldehydes in the presence of p-toluenesulfonic acid, in refluxing cyclohexane and under capture of water produced during the reaction, the enamine derivatives of general formula LV are obtained. Subsequent ring closure is achieved on heating at 250 °C in a high boiling solvent such as Dowtherm A to give compounds of general formula V. Transformation to the corresponding chloro quinoline derivatives of formula VI is performed on treatment with POCl3 under reflux, a standard method known in the literature. Subsequent neaction with corresponding, amines as defined above, either using a large excess of amine without solvent or on reaction with a 2-fold access, in a suited solvent such as ethanol or THF and in the presence of catalytic amounts of NaI and with pyridine as a base, gives compounds of formula VII<sub>1</sub>. The amines used are either substituted with R⁴, R⁵ groups as defined or the groups can be introduced by functional

group conversion as known in the art. P is a protecting group such as benzyl, ally or tert butyl. Deprotection under standard conditions known in the art gives rise to Ia<sub>1</sub>. Compounds of formula Ia<sub>1</sub> can also be obtained from the corresponding methoxy derivatives (P=Me, formula VII<sub>1</sub>) on methyl ether cleavage with BBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> as a solvent.

#### Scheme 4

R<sup>3</sup> is hydrogen or alkyl;

P is a protecting group such as e.g. benzyl, allyl or tert.butyl; R' is methyl or ethyl.

Compounds of general formula  $Ib_1$  and  $II_1$  ( $R^3$  not  $NH_2$ -, alkylamino, dialkylamino or alkoxy) are prepared as described above from appropriately substituted anilines according to scheme 4.

Compounds of formula  $\text{Ta}_2$ , with  $\text{R}^3$  equaling  $\text{NH}_2$ , alkylamino, dialkylamino can be prepared from anilines of formula III, by condensation with alkyl cyanoacetates, ring closure and subsequent functional group transformations as described above. The corresponding compounds with alkylamino or dialkylamino as  $\text{R}^3$  substitutents can be obtained from, for example, intermediate IX or  $\text{VII}_2$  ( $\text{R}^3$ =  $\text{NH}_2$ ) by selective N-alkylation.

In analogy to the sequence described in scheme 5 and starting from the appropriate anilines there can be obtained the compounds of fomula Ib<sub>2</sub> and II<sub>2</sub> (R<sup>3</sup> equaling NH<sub>2</sub>- or alkylamino or dialkylamino).

Scheme 5, - At us described above from energy mately substituted and lines according

R³ is NH2-, alkylamino or dialkylamino;

R' is methyl or ethyl;

P is a protecting group such benzyl, allyl or tert.-butyl

A further method to prepare compounds of general tormula Ia<sub>2</sub>, Ib<sub>2</sub> and II<sub>2</sub> comprises condensation of anilines of formula III with malonic esters to give compounds of formula X. Subsequent ring closure provides the 2,4-dihydroxyquinolines of general formula XI. Subsequent chlorination with POCl<sub>3</sub> gives then the 2,4-dichloro- quinolines of formula XII which can be selectively transformed to compounds of type VII<sub>2</sub> by sequential substitution reactions with the corresponding amines- in analogy to known reactions in the literature. By this procedure there can also be obtained compound of formula VII<sub>2</sub> (R<sup>3</sup> is alkoxy) via sequential treatment of XII with correponding amines and alkohols. The compounds Ib<sub>2</sub>, II<sub>2</sub> can be prepared in analogy according to scheme 6.

# 10 Preferred procedures are according to schemes 1, 2 and 5.

#### Scheme 6

in analysis accountable principles

R<sup>3</sup> is NH<sub>2</sub>: , alkylamino, dialkylamino or alkoxy;

R' is methyl or ethyl;

R" is methyl or ethyl

The conversion of a compound of formula I into a pharmaceutically acceptable salt can be carried out by treatment of such a compound with an inorganic acid, for example a hydrohalic acid, such as, for example, hydrochloric acid or hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid etc., or with an organic acid, such as, for example, acetic

acid, citric acid, maleic acid, fumaric acid, tartaric acid, methanesulfonic acid of p-toluenesulfonic acid. The corresponding carboxylate salts can also be prepared from the compounds of formula Tby treatment with physiologically compatible bases.

The conversion of compounds of formula I into pharmaceutically usable esters or amides can be carried out e.g. by treatment of suited amino or hydroxyl groups present in the molecules with an carboxylic acid such as acetic acid, with a condensating reagent such as benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) or N,N-dicylohexylcarbodiimide (DCCI) to produce the carboxylic ester or carboxylic amide.

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A preferred process for the preparation of a compound of formula I comprises one of the following reactions:

a) reaction of a compound of the formula la in the presence of a compound of the formula R1-Ha1 reaction of a compound of the formula R2-Ha1 reaction of a compound of the formula R1-Ha1 reaction of a compound of the formula R2-Ha1 reaction of the formula R3-Ha1 reaction of the f

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wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and A are as defined before and Hal is halogen; or

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b) Pd catalyzed C/O, C/N or C/C bond forming reaction of a compound of formula Ic in order to obtain a compound of formula T

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wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and A are defined as before and Hal is halogen, preferably chloro, bromo or iodo. Preferred is the reaction of a compound according to

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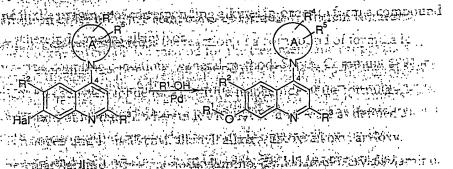
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formula Ic under Buchwald conditions (S. L. Buchwald in: J Am. Chem. Soc. 1996, p. 10333 and Acc. Chem Res. 1998, p.805 for the general method), particularly in the presence of Pd(OAc); BINAP and a base such as NaOtBu with a corresponding alkohol or amine in order to form a compound of formula I, wherein R2 means alkoxy or amino. Further preferred is the reaction of a compound of formula Ic under Suzuki-type coupling conditions (general method: Synth. Commun. 1991, p 513) in the presence of corresponding arylboronic acids or heteroarylboronic acids in order to form a compound of formula I, wherein R2 means aryl or heteroaryl. Also preferred is the reaction of a compound of formula Ic under Stille coupling conditions (for general method: Ang. Chem IE, 1986, 508) in the presence of corresponding arylstannanes or heteroarylstannanes in order to form a compound of formula I, wherein Rumeans aryl or heteroaryl. Further preferred is the reaction of a compound of formula Ic under Sonogashira conditions (review: Org. Preprine Proceed. Int. 1995, p127), particularly in the presence of Cul and a base such as triethylamine in the presence of corresponding alkines in order to form a compound of formula I, wherein R2 means alkinyl; or section of a compound of from use ic

a halogen/metal exchange reaction of a compound of formula Ic as defined in step b) and subsequent Pd catalyzed condensation with a halogenide of the formula R<sup>2</sup>-Hal to yield a compound of formula I, wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and A are as defined as before, Hal is halogen and R<sup>2</sup> is alkenyl, alkinyl, alkoxy, alkoxy, alkoxy, aryloxy, arylamino, heteroarylamino, NH<sub>2</sub>; monoalkylamino, dialkylamino, arylalkylamino, heteroarylalkylamino, arylalkoxy or heteroarylalkoxy.

d) reaction of a compound of formula II in the presence of an alcohol of the formula R<sup>1</sup>-OH and a palladium catalyst in order to obtain a compound of formula 1.



wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and A are defined as before, Hal is halogen and R<sup>1</sup> is hydrogen, alkyl, alkoxyalkyl, alkinyl, hydroxyalkyl, aralkyl, heterocyclylalkyl, cycloalkylalkyl, NH<sub>2</sub>-SO<sub>2</sub>-, monoalkylamino-SO<sub>2</sub>-, dialkylamino-SO<sub>2</sub>-, alkyl-SO<sub>2</sub>-,

aryl, NH<sub>2</sub>-alkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxycarbonylalkyl, carboxyalkyl, aryl-SO<sub>2</sub>-O-alkyl, cycloalkyl or cycloalkylalkyl.

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A particularly preferred process for the preparation of a compound of formula I comprises one of the reactions a), c) or d) as mentioned before.

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Preferred intermediates are:

7-benzyloxy-4-chloro-2-methyl-quinoline;

7-benzyloxy-6-butyl-4-chloro-quinoline hydrochloride;

6-bromo-4-chloro-7-methoxy-2-methyl-quinoline.

The compounds of formal and f

The compounds of formula I described above for use as therapeutically active substances are a further object of the invention.

Also an object of the invention are compounds described above for the production of medicaments for the prophylaxis and therapy of illnesses which are caused by disorders associated with the NPY receptor; particularly for the production of medicaments for the prophylaxis and therapy of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and objective.

Likewise an object of the invention are pharmaceutical compositions containing a compound of formula I described above and a therapeutically inert carrier.

An object of the invention is also the use of the compounds described above for the production of medicaments; particularly for the treatment and prophylaxis of arthritis, cardiovascular diseases; diabetes, renal failure and particularly eating disorders and obesity.

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A further object of the invention comprises compounds which are manufactured according to one of the described processes.

A further object of the invention is a method for the treatment and prophylaxis of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and obesity whereby an effective amount of a compound described above is administered.

According to a further aspect of the invention there is provided a method of treatment of obesity in a human in need of such treatment which comprises.

administration to the human a therapeutically effective amount of a compound according to formula I and a therapeutically effective amount of a lipase inhibitor, particularly preferred, wherein the lipase inhibitor is orlistat. Also subject of the present invention is the mentioned method, wherein the administration is simultaneous, separate or sequential.

o con long the first property and the first the control of the con A further preferred embodiment of the present invention is the use of a compound of the formula I in the manufacture of a medicament for the treatment and prevention of obesity in a patient who is also receiving treatment with a lipase inhibitor, particularly preferred, wherein the lipase inhibitor is orlistat.

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d. wherein the Phaseschild for is brilleday Also autique of the present invention is or come a method, wherein the advantagration is simultaneous, separate or

# Cloning of mouse NPY5 receptor cDNAs:

mandeling the state of the stat The full-length cDNA encoding the mouse NPY5 (mNPY5) receptor was amplified from mouse brain cDNA using specific primers, designed based on the published sequence, and Pfu DNA-Polymerase (Stratagene). The amplification product was subcloned into the mammalian expression vector pcDNA3 using Eco RI and XhoI restriction sites. Positive clones were sequenced and one clone, encoding the published sequence was selected for generation of stable cell clones. Sievel and a selection of another commerce arodure of a comment of another comments of the com

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# the second has the see in the form to consider, his o survived of the treatment invention is a second result of the survived has a stable transfection: The second results of the survived second sec

Human embryonic kidney 293 (HEK293) cells were transfected with 10 µg mNPY5 DNA using the lipofectamine reagent (Gibco BRL) according to the manufacturer's instruction. Two days after transfection, geneticin selection (1 mg/ml) was initiated and several stable clones were isolated. One clone was further used for pharmacological characterization. managatistististes as a second redivas using Eco. P. 1900 / high

### The description of stable call dones. Radioligand competition binding:

Human embryonic kidney 293 cells (HBK293), expressing recombinant mouse NPY5-receptor (mNPY5); were broken by three freeze/thawing cycles in hypotonic Tris 30

buffer (5 mM, pH 7.4, 1 mM MgCl<sub>2</sub>), homogenized and centrifuged at 72,000 x g for 15 min. The pellet was washed twice with 75 mM Tris buffer, pH 7.4, containing 25 mM MgCl<sub>2</sub> and 250 mM sucrose, 0.1 mM phenylmethylsulfonylfluoride and 0.1 mM 1,10-pheneanthrolin, resuspended in the same buffer and stored in aliquots at -80°C. Protein was determined according to the method of Lowry using bovine serum albumine (BSA) as a standard

Radioligand competition binding assays were performed in 250 µl 25 mM Hepes buffer (pH 7.4, 2.5 mM CaCl<sub>2</sub>, 1 mM MgCl<sub>2</sub>, 1 % bovine serum albumine, and 0.01 % NaN<sub>3</sub> containing 5 µg protein, 100 pM [125] labelled peptide YY (PYY) and 10 µL DMSO containing increasing amounts of unlabelled test compounds. After incubation for 1 h at 22 °C, bound and free ligand are separated by filtration over glass fibre filters. Non specific binding is assessed in the presence of 1 µM unlabelled PYY. Specific binding is defined as the difference between total binding and non specific binding. IC<sub>50</sub> values are defined as the concentration of antagonist that displaces 50 % of the binding of [125] labelled neuropeptide Y. It is determined by linear regression analysis after logit/log transformation of the binding data.

Results obtained in the foregoing test using representative compounds of the invention as the test compounds are shown in the following table to the compounds are shown in the following table.

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quinoline (example 5).
La Company Com
6-butyl-4-pymolidin 1-ylgomy set visite representations of the
quinolin-7-ol (example 34) olde in the following tables also must be in the following
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Preferred compounds as described above have  $IC_{50}$  values below 1000 nM; more preferred compounds have  $IC_{50}$  values below 100 nM, particularly below 10 nM. Most preferred compounds have  $IC_{50}$  values below 2 nM. These results have been obtained by using the foregoing test.

The compounds of formula I and their pharmaceutically usable salts and esters can be used as medicaments (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered internally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parentally, such as intramuscularly or intravenously (e.g. in the form of injection solutions).

The compounds of formula fand their pharmaceutically usable salts and esters can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées and hard gelatin capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées and hard gelatin capsules.

Suitable adjuvants for soft gelatin capsules, are, for example, vegetable oils, waxes, fats, semi-solid substantes and liquid polyols, etc. soft solutions are the control of the control

Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose invert sugar, glucose, etc.

Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, etc.

Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

In accordance with the invention the compounds of formula I and their pharmaceutically usable salts can be used for the prophylaxis and treatment of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and

obesity. The dosage can vary in wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 0.1 mg to 20 mg per kg body weight, preferably about 0.5 mg to 4 mg per kg body weight (e.g. about 300 mg per person); divided into preferably 1-3 individual doses, which can consist, for example, of the same amounts; should be appropriate. It will, however, be clear that the upper limit given above can be exceeded when this is shown to be indicated.

The invention is illustrated hereinafter by Examples, which have no limiting character.

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### Examples

### Example 1

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a) A mixture of 534 mg (1.8 mmol) of 7-benzyloxy-4-chloro-2-methyl-quinoline and 3.77 ml (45 mmol) pyrrolidine was heated at 80°C (oil bath temperature) under an argon atmosphere for 23 h after which time the reaction was completed according to HPLC analysis. The reaction was partitioned between EtOAc and water, the aqueous layer was extracted once with EtOAc, the combined organic layers were washed with water then saturated NaCl solution, dried over magnesium sulphate and concentrated in vacuo. The residue was applied to silica gel column with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH (19:1:0.05) as eluent. Combination of the purified fractions and concentration in vacuo gave 430 mg (74.5%) of the 7-benzyloxy-2-methyl-4-pyrrolidin-1-yl-quinoline as a brown solid. ISP mass spectrum, m/e: 319.4 (M+1 calculated for C<sub>2</sub>iH<sub>22</sub>N<sub>2</sub>O:319).

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### Preparation of the starting material:

b) 20 g (98.4 mmol) of 3-benyloxyaniline, 12.6 ml (0.984 mmol) of ethyl acetoacetate and 0.189 g (1 mmol) of p-toluenesulfonic acid monohydrate in 32 ml of cyclohexane were heated at reflux for 5.5 h in the presence of a water-separator funnel. The reaction mixture was cooled to RT, some solid material was filtered off by suction and the filtrate was concentrated in vacuo to give 30.6 g (99%) of the desired 3-(3-benzyloxy-phenylamino)-but-2-enoic acid ethyl ester as a yellow oil. This was used without further purification in the next reaction step.

c) 3.67 g (11.8 mmol) of 3-(3-benzyloxy-phenylamino)-but-2-enoic acid ethyl ester were added dropwise within 20 minutes to 5.5 ml of Dowtherm A heated at 250°C (metal bath temperature). The solution was stirred further 10 minutes at 250°C (bath temperature), cooled to RT and then treated with 20 ml of heptane. The brown viscous oil that had formed was isolated and triturated with 45 ml of AcOEt. The brown solid obtained was filtered off by suction, washed with AcOEt and dried in a high vacuum to give 1.19 g (35%) of 7-benzyloxy 2-methyl-quinolin-4-oil ISP mass spectrum, m/e. 266.3 (M+1 calculated for C<sub>17</sub>H<sub>15</sub>NO<sub>2</sub>: 266)

d) 1.15 g (3.99 mmol) of 7-benzyloxy-2-methyl-quinolin 4-ol in 7.46 ml (79.8 mmol) of POCl<sub>3</sub> were heated at 130°C (oil bath temperature) for 1h 40 min until completion of the

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reaction according to TLC analysis. The reaction mixture was cooled to RT and the solvent was removed in vacuo. The residue was taken up in ice water and stirred for 2.h. The pH was adjusted to values between pH 9-10 with concentrated NH<sub>4</sub>Cl, the brown solid which precipitated was filtered off by suction, washed with water and subsequently dried in a high vacuum. This gave 1 g (84.5%) of 7-benzyloxy-4-chloro-2-methyl-quinoline as a brown solid. EI mass spectrum, m/e: 283.1 (M+1 calculated for C<sub>17</sub>H<sub>14</sub>ClNO: 283).

#### Example 2

A solution of 13 g of 7-benzyloxy-2-methyl-4-pyrrolidin-1-yl-quinoline, product of example 1, dissolved in 750 ml of MeOH was treated with 4 g of palladium on charcoal (10%) and then hydrogenated at RT for 1.5 h until HPLC analysis indicated the completion of the reaction. The catalyst was filtered off, washed with water, and the solution was concentrated in vacuo. The solid that precipitated was collected by filtration and dried in a high vacuum to give 8.9 g. (96.2%) of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol as an amorphous yellow solid. ISP mass spectrum, m/e: 229.2 (M+1 calculated for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O: 229).

#### Example 3

229.4 mg (1 mmol) of 2 methyl 4 pyrrolidin 1-yl-quinolin-7-ol, product of example 2, were suspended under an argon atmosphere in 20 ml of DMF, 0.6 g (112 mmol) of recommolecular sieves (4 nm) were added followed by 138 mg (1,2 mmol) of potassium tertbutoxide, and the mixture was stirred for 1 h at RT. It was then cooled to 0°C, created with 0.13 ml (1.2 mmol) N,N-dimethylsulfamoylchloride and stirred for 3 hat 0°C. The reaction mixture was partitioned between EtOAc and water, the aqueous layer was extracted twice with EtOAc, the combined organic layers were washed with water then with saturated NaCl solution, dried over magnesium sulphate and concentrated in vacuo. The residue was triturated with diethyl ether; the viscous oil obtained was filtered off by suction and dried in a high vacuum. Upon further triturating with heptane solid material was obtained which was dried in a high vacuum to give 100 mg (29.3%) of dimethyl-sulfamic acid 2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl ester as an off-white solid. ISP mass spectrum, m/e; 336.2 (M+1 calculated for C<sub>16</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>S; 336).

In analogy to example 3, from 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 2, and methanesulfonyl chloride there was obtained methanesulfonic acid 2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl ester as an off-white solid. ISP mass spectrum, m/e: 307.3 (M+1 calculated for Ci-H<sub>18</sub>N<sub>3</sub>O<sub>3</sub>S=307).

### Example 5

्रीत प्रतिकारिक विक्रिके के विद्योगित हैं किये का कार्य का तर के साथ पर प्रतिकार की कार्य का कार्य के कार्य की कार्य के अपने कार्य की के से किसी की की की कार्य की की की कार्य के की मान की की

In analogy to example 3, from 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 2, and cyclopropylmethyl bromide - with reaction times of 19 h (0°C) and isolation of the product as hydrochloride via treatment of the reaction product with HCl-saturated diethyl ether - there was obtained 7-cyclopropylmethoxy-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a white solid. ISP mass spectrum, m/e: 283.2 (M+1 calculated for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O: 283)

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A mixture of 114 mg (0.5 mmol) of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 2, 166 mg (0.6 mmol) of potassium carbonate and 84 µl (0.6 mmol) of 3-methoxybenzyl chloride was heated at 80°C in 8 ml of DMF under an argon atmosphere for 23 h. The mixture was cooled to RT and partitioned between EtOAc and water. The organic layer was separated, washed with water then saturated NaCl solution, dried over magnesium sulphate and concentrated in vacuo. The residue was taken up in diethyl ether and some not dissolved material was removed by filtration. The filtrate was treated under stirring with 0.25 ml of 3N HCL in MeOH and stirring was continued for 1h. The solid that precipitated was filtered off by suction and dried in a high vacuum to give 138 mg (69.7%) of 7-(3-methoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as an light-yellow solid. ISP mass spectrum, m/e-349.4 (M+1 calculated for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: 349).

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In analogy to example 6 there was prepared; on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with methyl iodide, 7-methoxy 2-methyl 4-pyrrolidin-1-yl-quinoline.

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hydrochloride as an off-white solid. ISP mass spectrum, m/e: 243.3 (M+1 calculated for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O: 243).

### Example 8

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-picolyl choride, whereby the product was isolated as free base, 2-methyl-7-(pyridin-2-ylmethoxy)-4-pyrrolidin-1-yl-quinoline as a light brown solid. ISP mass spectrum, m/e: 320.4 (M+1 calculated for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O: 320).

### Example 9

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In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with allyl bromide, whereby the product was isolated as free base, 7-allyloxy-2-methyl-4-pyrrolidin-1-yl-quinoline as a light yellow solid. EI mass spectrum, m/e: 268.2 (M calculated for C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O: 268)

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In analogy to example 6 there was prepared on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with isobityl bromide, 7-isobitoxy-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a white solid. ISP mass spectrum, m/e: 285.3 (M+1 calculated for C<sub>18</sub>H<sub>24</sub>N<sub>2</sub>O: 285).

### Example 11

or of the Afril bedoming a remerence the resolution and isolated as free bage. Wall where

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In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-methoxybenzyl chloride, 7-(2-methoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as an off-white solid. ISP mass spectrum, m/e: 349.4 (M+1 calculated for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: 349).

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with tetrahydro-furfuryl bromide, whereby the product was isolated as free base, (rac) 2-methyl-4-pyrrolidin-1-yl-7-(tetrahydro-furan-2-ylmethoxy)-quinoline as a yellow-brown waxy solid: ISP mass spectrum, m/e: 313:2 (M±1 calculated for C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: 313).

### Example 13

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In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with of 4-methoxybenzyl chloride, 7-(4-methoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a light-yellow solid. ISP mass spectrum, m/e: 349.4 (M+1 calculated for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: 349).

#### Example 14

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-bromomethyl benzonitrile, whereby the product was isolated as free base, 2-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile as a brown solid. ISP mass spectrum, m/e: 344.4 (M+1 calculated for C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O: 344).

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of a 7-1 was of 4-method percent the mit. The method benevices 1.2 and hel-4-

In analogy to example 6 there was prepared; on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 4-bromomethyl benzonitrile whereby the product was isolated as free base, 4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile as a brown solid. ISP mass spectrum, m/e: 344.4 (M+1 calculated for C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O: 344).

### Example 16-3 or H

a philipsetting inequalities in particular tengent who received as the

regraphicate it of employing temporary method chepsonitrie as a become

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-(trifluoromethyl)-benzyl-chloride, 2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyrrolidin-1-yl-7-(2-methyl-4-pyr

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trifluoromethyl-benzyloxy)-quinoline hydrochloride as a white solid. ISP mass spectrum, m/e: 387.4 (M+1 calculated for C<sub>22</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: 387).

### Example 17

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In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with of 3-(trifluoromethyl)-benzyl chloride, 2-methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethyl-benzyloxy)-quinoline hydrochloride as an off-white solid. ISP mass spectrum, m/e: 387.4 (M+1 calculated for C<sub>22</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: 387).

g --- ethyl-bentriosy i-quincilia biodischlotide av white-solid. The mask spectrum.

to the Academia of Carlos Example 18

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with of 4-(trifluoromethyl)-benzyl chloride, 2-methyl-4-pyrrolidin-1-yl-7-(4-trifluoromethyl-benzyloxy)-quinoline-hydrochloride as an off-white solid. ISP mass spectrum, m/e: 387 4 (M+1 calculated for C<sub>22</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: 387).

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### West calculated (<u>Example 19</u>%)

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-chlorobenzyl chloride, 7-(2-chloro-benzyloxy)-2-methyl-4-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a whitesolid. ISP mass spectrum, m/e: 353.3 (M+1 calculated for C<sub>21</sub>H<sub>21</sub>ClN<sub>2</sub>O: 353).

### Example 20

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In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 3-chlorobenzyl chloride, 7-(3-chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 353.3 (M+1 calculated for C<sub>21</sub>H<sub>21</sub>ClN<sub>2</sub>O: 353).

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 4-chlorobenzyl chloride, 7-(4-chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as an off-white solid. ISP mass spectrum, m/e: 353.3 (M+1 calculated for  $C_{21}H_{21}ClN_2O$ : 353).

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### Example 22

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 3-(chloromethyl)pyridine hydrochloride, whereby the product was isolated as free base, 2-methyl-7-(pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline as a red solid. ISP mass spectrum, m/e: 320.4 (M+1 calculated for C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O: 320).

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In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 3-bromomethyl benzonitrile, whereby the product was isolated as free base, 3-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile as a yellow solid. ISP mass spectrum, m/e: 344.4 (M+1 calculated for C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O: 344).

# P mass spectrum in a bid Example 24 mater and the control of the c

In analogy to example 6 there was prepared: on reaction of 2 methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-bromopropane; 7-isopropoxy-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a light-yellow solid. ISP mass spectrum, m/e: 271.4 (M+1 calculated for C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O: 271).

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In analogy to example 6 there was prepared; on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 1-bromo-2-methoxyethane, 7-(2-methoxy-ethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a light-brown solid. ISP mass spectrum, m/e: 287.2 (M+1 calculated for C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: 287).

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In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 4-(2-chloroethyl)-morpholine hydrochloride, whereby the product was isolated as free base, 2-methyl-7-(2-morpholin-4-yl-ethoxy)-4-pyrrolidin-1-yl-quinoline as a brown solid. ISP mass spectrum, m/e: 342.3 (M+1 calculated for C<sub>20</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>; 342).

### Example 27

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In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 4-(chloromethyl)pyridine hydrochloride, 2-methyl-7-(pyridin-4-ylmethoxy)-4-pyrrolidin-1-yl-quinoline, hydrochloride as a light-yellow solid. ISP mass spectrum, m/e: 320.4 (M+1 calculated for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O: 320).

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armolin-1-ol with 4-12-chlorograph-guilthanasti repeablither, whereby the productives

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a) A mixture of 436 mg (1.5 mmol) of 7-Benzyloxy 4-chloro-2-methyl-quinoline, product of example 1d), and 1.75 g (15 mmol) of (S)-3-ethoxypyrrolidine, prepared according to Tetrahedron Lett., 1995, 2745, was heated at 80°C (oil bath temperature) under an argon atmosphere for 18 h after which time the reaction was completed according to HPLC analysis. The excess (S)-3-ethoxy pyrrolidine was distilled off, and the residue was partitioned between EtOAc and water. The layers were separated, the organic layer was washed with water then saturated NaCl solution, dried over magnesium sulphate and concentrated in vacuo. The residue was taken up in MeOH (1ml) diluted with diethyl ether (30 ml) and then treated dropwise at RT under stirring with 0.7 ml of 3N HCL in MeOH. The solvent was removed and the remaining salt triturated with diethyl ether, then filtered off by suction and dried in a high vacuum to give 425 mg (69.7%) of the (S)-7-benzyloxy-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 363.2 (M+1 calculated for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>: 363).

A solution of 93 mg (0.23 mmol) of (S)-7-Benzyloxy-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinoline hydrochloride; product of example 28, dissolved in 7 ml of MeQH was treated with 48 mg of palladium on charcoal (10%) and then hydrogenated at RT for 1.5 h until HPLC analysis indicated the completion of the reaction. The catalyst was filtered off, washed with water, and the solution was concentrated in vacuo. The residue was triturated with n hexane / diethyl ether; the solid obtained was filtered off by suction and dried in a high vacuum to give 67mg (90%) of (S)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride as an off-white solid. ISP mass spectrum, m/e: 273.3 (M+1 calculated for  $C_{16}H_{20}N_2O_2$ : 273).

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#### Example 30

In analogy to example 6, on reaction of (S)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride, product of example 29, with 3-methoxybenzyl chloride there was obtained: (S)-4-(3-ethoxy-pyrrolidin-1-yl)-7-(3-methoxy-benzyloxy)-2-methyl-quinoline hydrochloride as a white solid ISP mass spectrum, m/e: 393.3 (M+1 calculated for  $C_{24}H_{28}N_2O_3$ : 393).

#### Example 31

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In analogy to example 6, on reaction of (S)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride, product of example 29, with 4-bromomethyl benzonitrile there was obtained: (S)-4-[4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yl) yloxymethyl]-benzonitrile hydrochloride as a yellow solid. TSP mass spectrum, m/e: 388.3 (M+1 calculated for C<sub>24</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>, 388)

### Example 32 persons and a supple service of the serv

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In analogy to example 6, on reaction of (S)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride, product of example 29, with 2-bromomethyl benzonitrile there was obtained: (S)-2-[4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile hydrochloride as a light-orange solid. ISP mass spectrum, m/e: 388.3 (M+1-calculated for C24H2-N3Q2: 388); +

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### Example 33

a) A solution of 1g (3.07 mmol) of 7-benzyloxy-6-butyl-4-chloro-quinoline hydrochloride in 2.5 ml (30.7 mmol) of pyrrolidine was heated at 60°C with stirring under an argon atmosphere for 24 h after which time the reaction was completed according to HPLC analysis. The excess pyrrolidine was evaporated off, and the residue was partitioned between EtOAc and water. The layers were separated and the aqueous layer once extracted with AcOEt. The combined organic layers were washed with water then saturated NaCl solution, dried over magnesium sulphate and concentrated in vacuo to give 1.12 g (97.4 %) of the 7-benzyloxy-6-butyl-4-pyrrolidin-1-yl-quinoline as a brown oil. ISP mass spectrum, m/e: 361.3 (M+1 calculated for C<sub>24</sub>H<sub>28</sub>N<sub>2</sub>O: 361).

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Preparation of the starting material; - penzylasy-6-bury-4-gulore-sain of re-hyprochlorid-

b) A suspension of 1.75 g (5 mmol) of 7-benzyloxy-6-butyl-4-oxo-1.4-dihydro-quinoline-3-carboxylic acid (prepared from methyl benzoquate on ester hydrolysis with KOH in EtOH-H<sub>2</sub>O) in 9 ml of quinoline was treated with 57 mg (0.9 mmol) of Cu powder and heated for 1 h at 200 °C. The black reaction mixture was cooled to RT, 80 ml of diethyl ether were added and the solid which precipitated was filtered off by suction. It was then taken up in 100 ml of MeOH, heated to reflux and filtered hot. The filtrate was then concentrated in vacuo. The residue was triturated with diethyl ether, filtered off by suction and dried in a high vacuum to give 966 mg (63 %) of the 7-benzyloxy-6-butyl-1H-quinolin-4-one as a light-yellow solid. ISP mass spectrum, m/e: 308.3 (M+1 calculated for C<sub>20</sub>H<sub>21</sub>NO<sub>2</sub>: 308).

c) A suspension of 900 mg (2.93 mmol) of 7-benzyloxy-6-butyl-1H-quinolin-4-one in 1.44 ml of POCl<sub>3</sub> (15.8 mmol) was treated with 0.074 ml of N,N-dimethylaniline and heated at 60°C for 3 h with stirring. The reaction mixture was then poured into ice water and stirred for 0.5 h. The solid which precipitated was filtered off by suction washed with water and dried in a high vacuum to give 1.05 g (99%) of 7-benzyloxy-6-butyl-4-chloro-quinoline hydrochloride as light gray solid 1SP mass spectrum; m/e: XX (M+1 calculated for C<sub>20</sub>H<sub>20</sub>ClNO: 325.84):

A solution of 1.02 g (-2.83 mmol) of the 7-benzyloxy-6-butyl-4-pytrolidin-1-yl-quinoline. product of example 33; dissolved in 50 ml of MeOH was treated with 0.33 g of palladium on charcoal (10%) and then hydrogenated at RT for 2h until TLC analysis indicated the completion of the reaction. The catalyst was filtered off, the solution was concentrated in vacuo and the residue was dried in a high vacuum to give 0.65 g (82 %) of the 6-butyl-4pyrrolidin-1-yl-quinolin-7-ol as a light yellow solid: ISP mass spectrum, m/e: 271.3 (M+1 calculated for C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O. 271)

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### Example 35

In analogy to example 6; on reaction of 6-butyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 34, with methyl iodide chiloride there was obtained 6 butyl- 7 methoxy 4 vince pyrrolidin-1-yl-quinoline hydrochloride as a waxy brown solid ISP mass spectrum, in/e: 285.3 (M+1 calculated for C18H2/N2O:285) and the distribution in the the

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### Example 36 What she are say the say and the say of the

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In analogy to example 6, on reaction of 6-butyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 34, with ethyl iodide chloride there was obtained: 6-butyl-7-ethoxy-4-----pyrrolidin-1-yl-quinoline hydrochloride as an amorphous yellow solid. ISP mass spectrum, m/e: 299.4 (M+1 calculated for C19F126N2O: 299).

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In analogy to example 6, on reaction of 6-butyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 34, with bromomethyl cyclopropane there was obtained: 6-butyl-75 cyclopropylmethoxy-4-pyrrolidin-1-yl-quinoline hydrochloride as an off-white solid. ISP mass spectrum, m/e: 325.3 (M+1 calculated for C<sub>21</sub>H<sub>28</sub>N<sub>2</sub>O: 325).

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In analogy to example 6, on reaction of 6-butyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 34, 4-bromomethyl benzonitrile there was obtained: 4-(6-butyl-4-pyrrolidin-1-

yl-quinolin-7-yloxymethyl)-benzonitrile as a light yellow solid. ISP mass spectrum, m/e: 386.4 (M+1 calculated for C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>O: 386).

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### Example 39

a) A solution of 2 g (6.9 mmol) of 7-benzyloxy-4-chloro-2-methyl-quinoline product of 5 example 1d), in 15.5 ml (0.137 mol) of hexamethyleneimine was heated at 120 °C (oil bath temperature) with stirring under an argon atmosphere for 100 h after which time the reaction was completed according to HPLC analysis. The reaction mixture was cooled to RT and then partitioned between EtOAc and water. The layers were separated the aqueous layer once extracted with AcOEt. The combined organic layers were washed with water 10 then saturated NaCl solution, dried over magnesium sulphate and concentrated in vacuo. The oily residue was dissolved in a small amount of MeOH and treated under stirring with 4 ml of 3N HCl in MeOH. The solvent was removed in vacuo, the residue triturated with diethyl ether under stirring for 1.5 h and the obtained solid-filtered off by suction and dried in a high vacuum. (Further material was obtained on evaporation of the filtrate and 15 treatment of the residue as described above). The desired 4-azepan-I-yl.7 henzyloxy-2methyl-quinoline hydrochloride, 1.46.g (55.2-%) was thus obtained as a light brown solid. ISP mass spectrum, m/e: 347.4(M±1 calculated for C23H26N2O: 347).

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### Example 40

A solution of 1.45 g (3.78 mmol) of 4-azepan-1-yl-7-benzyloxy-2-methyl-quinoline hydrochloride, product of example 39, dissolved in 120 ml of MeOH was treated with 700 mg of palladium on charcoal (10%) and then hydrogenated at RT for 2 h until HPLC analysis indicated the completion of the reaction. The catalyst was filtered off, washed with water, and the solution was concentrated in vacuo. The residue was triturated with diethyl ether, the solid obtained was filtered off by suction and dried in a high vacuum to give 1 g (90.4%) 4-azepan-1-yl-2-methyl-quinolin-7-ol hydrochloride as a light gray solid. ISP mass spectrum, m/e: 257.2 (M+1 calculated for C16H20N2O: 257).

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#### Example 41

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In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-oboline hydrochloride, product of example 40, with 4-(chloromethyl) pysidine hydrochloride there

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was obtained: 4-azepan-1-yl-2-methyl-7-(pyridin-4-ylmethoxy)-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 348.4 (M+1 calculated for C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O: 348). A 125 mandy of 1001, was heared at 900 with 10 to waste suprime. It was then conded 48).

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In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-ol hydrochloride, product of example 40, with 4-bromomethyl benzonitrile there was obtained: 4-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile hydrochloride as a light yellow solid. ISP mass spectrum; m/e: 372.3 (M+1 calculated for C24H25N3O: 373). The same street of the s

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Example 43

In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-ol hydrochloride, product of example 40, with 3-bromomethyl benzonitrile there was obtained: 3-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 372.3 (M+1 calculated for C<sub>24</sub>H<sub>25</sub>N<sub>3</sub>O: A STATE OF THE PROPERTY OF THE

## Fig. commed 4-viscours but-2-methyl Example 44 stantages - unique by tractioning

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particles of the second of the In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-ol--20 hydrochloride, product of example 40, with 2-(chloromethyl)pyridine hydrochloride there was obtained: 4-azepan-1-yl-2-methyl-7-(pyridin-2-ylmethoxy)-quinoline hydrochloride as a light yellow solid. ISP mass spectrum; m/e: 348.5 (M+1 calculated for C22H25N3O: 348). A second for a control of the second for the second for the second field of the second for the second for

## Example 45 Example 45

a) A suspension of 1 g (3.5 mmol) of 6-bromo-4-chloro-7-methoxy-2-methyl-quinoline in 20 ml of EtOH was treated sequentially at RT and under stirring with 0.49 g (7 mmol) of pyrrolidine, 0.137 g (1.4 mmol) of pyridine and a catalytic amount of NaI. The mixture was then heated to reflux for 20th, cooled to RT and concentrated in vacuo. The residue

was applied to a silica gel column with CH<sub>2</sub>Cl<sub>2</sub>/MeOH (7:1) as eluent. Combinations of the purified fractions and concentration in vacuo gave 0.85 g (68.2%) of the 6-bromo-7-methoxy-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as light brown solid. ISP mass spectrum, m/e: 323.3 (M+1 calculated for C<sub>15</sub>H<sub>17</sub>BrN<sub>2</sub>O: 323).

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Preparation of the starting material:

b) 7.66 g (37.9 mmol) of 4-bromo-3-methoxy-phenylamine (preparation described in Tetrahedron Lett., 1995, 7583) were dissolved in 80 ml of cyclohexane at 70°C and subsequently treated under stirring with 72 mg (0.38 mmol) of p-toluenesulfonic acid monohydrate and 4.93 g (37.9 mmol) of ethyl acetoacetate. The solution was then heated at reflux for 3.5 h with a water separator funnel connected. It was then cooled to RT and concentrated in vacuo. The residue was applied to a silica gel column with hexane/diethyl ether (3.1) as eluent. Combinations of the purified fractions and concentration in vacuo gave 8.2-g (68.8%) of the (Z) 3-(4-bromo-3-methoxy-phenylamino)-but-2-enoic acid ethyl ester, as a yellow solid. ISP mass spectrum, m/e: 316.2(M+1 calculated for C<sub>13</sub>H<sub>16</sub>BrNO<sub>3</sub>: 316).

c) A suspension of 6.6-g (21 mmol) of (Z)-3-(4-bromo-3-methoxy-phenylamino) but-2-enoic acid ethyl ester in 40 ml of Dowtherm A were heated under stirring at 220°C for 7-5 h after which time TLC analysis indicated completion of the reaction. The mixture was cooled to RT under stirring and the solvent was decanted off. The remaining solid residue was triturated with hexane afflered off by suction and dried in a high vacuum to give 4-7 g (84%) of the 6-bromo-7-methoxy-2-methyl-quinolin-4-olias a dark brown solid. El mass spectrum, m/e: 269 M calculated for Childholm NO2 269)

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d) A suspension of 4.6 g (17.5 mmol) of 6-bromo-7-methoxy-2-methyl-quinolin-4-ol in 14.8 ml (158 mmol) of POCl<sub>3</sub> was heated at 60°C for 20 h with stirring. It was then cooled to RT and 50 ml of diethyl ether were added. The solid that precipitated was filtered off by suction and dried in a high vacuum to give 3.85 g of the 6-bromo-4-chloro-7-methoxy-2-methyl-quinoline as a dark brown solid. El mass spectrum m/e: 287 (M calculated for C<sub>11</sub>H<sub>9</sub>BrClNO: 287)

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A solution of 115 mg (0.32 mmol) of 6-bromo-7-methoxy-2-methyl-4-pyrrolidin-1-yl-... quinoline hydrochloride, compound of example 45 a), was dissolved in 5 ml of dry CH2Cl2 under an argon atmosphere and treated dropwise with 0.16 g (0:64 minol) of 1M BBr3 in CH2Cl2 with ice cooling. After 0.5 h the ice bath was removed, the solution was stirred for 2 h at RT and then heated to reflux for 12 h. The reaction mixture was cooled to RT and partitioned between ice water and GH2Cl2. The layers were separated, the aqueous layer The combined organic layers were dried over magnesium sulphate and concentrated in vacuo. The residue was applied to a silica gel column with CH<sub>2</sub>Cl<sub>2</sub>/MeOH (15:1) as eluent. 10 Combinations of the purified fractions and concentration in vacuo gave 39 mg (35%) of the 6-bromo-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol hydrochloride as a light brown solid, ISP-mass spectrum, m/e: 307.2 (M+1 calculated for C1/H15B1N-O: 307); a chaithe brainchne ide, each gollacht a <del>leachtale l</del>e the was alst als ar each or ar in ar ar cui. ार सहिता । विकास कार केर की है के हैं जो हैं के हैं के हैं के हैं के कि कि केर केर केर केर केर केर केर केर के CPHOTO with for cholica National Warner Example 47, the noveletter contribution was entreprise 15 In analogy to example 6, on reaction 6-bromo-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol hydrochloride, product of example 46, with 4-bromomethyl benzonitile there was obtained: 4-(6-bromo-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile as a light yellow solid ISP mass spectrum, m/e: 424.3 (M+1) calculated for C22H20BrN3O 424). The resets springlifed due since set to grant with the total feld it is seen our. 20 Compliquents at the graphed leachings and godicentration in value give 35 mg (35%) of the A-forest in the demonstration by the confidence of the confide Example 48 plan to the first which is a few and a second of the second o 2. a) Assolution of 319 mg (0.92 mmol) of 4-chloro-7 methoxy-quinolin-2-ylamine in 20 ml of isopropanol was treated with 130 mg (1.83 mmol) of pyrrolidine and heated at 60°C for 6 h. The reaction mixture was cooled to RT, concentrated in vacuo. The residue was applied to a silica gel column with hexane/AcOEr (1:1) as eluent. The purified fractions were combined and concentrated in vacuo upon which the desired product crystallized out. The crystals were filtered off and dried in a high vacuum to give 48 mg (21%) of 7 methoxy-4-pyrrolidin-1-yl-quinolin-2-ylamine hydrochloride as a light brown solid: El mass spectrum, m/e: 243:2 (M calculated for GaHi/NaOs 243) gration were entitle throughout floregions wild about anticipion on cause of the 1950s of The section of a regular desperance of the first light of the section of a side as a figuration of the section of b) Above used starting material was obtained from commercially available 1-(4-chloro-7methoxy-2-quinolyl)=3-phenylurea (500 mg 11:53 mmol) on heating in a solution of

isopropanol/THF/CH2Cl2 (30 ml: 20 ml) and in the presence of 217 mg (3 mmol) of pyrrolidine for 12 h at 60°C. Upon concentration of the reaction mixture the desired product crystallized out. It was filtered off by suction and dried in a high vacuum to give 250 mg (78%) of the 4-chloro-7-methoxy-quinolin-2-ylamine as a light brown solid. ISP mass spectrum, m/e: 208.1 (M-calculated for C10H9ClN2O: 208).

## on the second and the first of the property of the filter of the second Example 49

In analogy to example 45 a), from 4-chloro-7-methoxyquinoline (synthesis described in: J. Med. Chem., 1998, 4918) and pyrrolidine there was obtained: 7-methoxy-4-pyrrolidin-1yl-quinoline hydrochloride as a yellow solid. ISP mass spectrum, m/e: 229.2 (M+1 calculated for  $C_{14}H_{16}N_{2}O$ : 229). Adole Box III Bill EVECT (Epon epidergroup) aloutile a personicament in edestred (

The me Third of the Archory Transport during 1-yearns and help become old USP Example 50

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In analogy to example 46, from 7-methoxy-4-pyrrolidin-1-yl-quinoline hydrochloride and on treatment with BBr3 in toluene under reflux there was obtained was obtained: 4pyrrolidin-1-yl-quinolin-7-ol as a brown solid. ISP mass spectrum, m/e: 215.3 (M+1) calculated for  $C_{13}H_{14}N_2O$ : 215).

'- an slow torexample 45 at from 4-shipp-7 biethorrquisoline (senthesis described in fra. Cl and 1988, 4913) and pyriolidine magnwas obtaine (1) -methop -4-pyrrolidin-1consine have ochionide as a velice and seample 51 as section and 229 1 81-1 and of

In analogy to example 6 there was prepared; on reaction of 2-methyl-4-pyrrolidin-1-ylquinolin-7-ol with 3,5-dimethoxybenzyl chloride, 7-(3,5-dimethoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 379.4 (M+1 calculated for  $C_{23}H_{26}N_2O_3$ : 379)

oposev menample 40. from 7-methory. 40 methory are billing-1-y-quancime inversectionide and त अन्यक्षणान्याः स्टार्गतः निवन्तांकार्यास्त्रात्त्रात्त्रात्त्रात्त्रात्त्रात्त्रात्त्रात्त्रात्त्रात्त्रात्त त अन्यक्षणान्याः स्टार्गतः निवन्तांकर्यास्त्रात्त्रात्त्रात्त्रात्त्रात्त्रात्त्रात्त्रात्त्रात्त्रात्त्रात्त

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In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-ylquinolin-7-ol with 3,4-dimethoxybenzyl chloride, whereby the product was isolated as free base. 7-(3.4-dimethoxy-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline as a light yellow solid ISP mass spectrum; in/e::379.4 (M+f calculated for C2:H2:N2O3: 379)...

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### Example 53

In analogy to example 6 there was prepared; on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with ethyl iodide, whereby the product was isolated as free base, 7-ethoxy-2-methyl-4-pyrrolidin-1-yl-quinoline as a brown solid ISP mass spectrum, m/e: 257-1 (M+1 calculated for  $C_{16}H_{20}N_2O$ : 257)

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In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 6-methyl-2-chloromethyl-pyridine, 2-Methyl-7-(6-methyl-pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline hydrochloride as off-white solid. ISP mass spectrum, m/e: 334,3 (M+1 calculated for C<sub>21</sub>H<sub>23</sub>N<sub>3</sub>O: 334).

### in analogy to example without Widelifepared in a read final 2-methyly-portolidin-1-vilnamelin-7-obsity sthyliodiste, whereh Example 55 transpolated as dee base, 7-eth my-2-

In analogy to example 6 there was prepared on reaction of 2 methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-methyl-3-chloromethyl-pyridine, 2-methyl-7-(2-methyl-pyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline hydrochloride as light yellow solid. ISP mass spectrum, m/e: 334.3 (M+1 calculated for C21H23N3O: 334).

### Example 56

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In analogy to example 6 there was prepared; on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 6-chloro-3-chloromethyl-pyridine, 7-(6-chloro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as white solid. ISP mass spectrum, m/e: 354.2 (M+1 calculated for  $C_{20}H_{20}ClN_3O$ : 354).

### Example 57

In analogy to example 6 there was prepared on reaction of 2 methyl-4 pyriolidin-1-yl-quinolin-7-ol with 2-chloro-3-chloromethyl-pyridine, 7-(2-chloro-pyridin-3-ylmethoxy)-2-methyl-4-pyriolidin-1-yl-quinoline hydrochloride as white solid: ISP mass spectrum, m/e: 354.3 (M+1 calculated for C<sub>20</sub>H<sub>20</sub>ClN<sub>3</sub>O: 354).

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In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 3-chloromethyl-2-fluoro-pyridine, 7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as white solid. ISP mass spectrum, m/e: 338.2 (M+1 calculated for C<sub>20</sub>H<sub>20</sub>FN<sub>3</sub>O: 338).

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In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-chloro-3-chloromethyl-6-methyl-pyridine, 7-(2-chloro-6-methyl-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as light yellow solid. ISP mass spectrum, m/e: 368.2 (M+1 calculated for C<sub>21</sub>H<sub>22</sub>ClN<sub>3</sub>O: 368).

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In analogy to example 6 there was prepared, on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 3-bromomethyl-2-chloro-6-trifluoromethyl-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline as a white solid. ISP mass spectrum, m/e: 422.2 (M+1 calculated for C<sub>21</sub>H<sub>19</sub>ClF<sub>3</sub>N<sub>3</sub>O: 422).

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### Example 62

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In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 2-chloro-5-chloromethyl-thiophene, 7-(5-chloro-thiophen-2-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline-hydrochloride as white solid. ISP mass spectrum, m/e: 359.2 (M+1 calculated for CoHpGIN-OS 359)

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### Example 63

In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 3-chloromethyl-thiophene, 2-methyl-4-pyrrolidin-1-yl-7-(thiophen-3-ylmethoxy)-quinoline hydrochloride as white solid. ISP mass spectrum, m/e: 325.4 (M+1 calculated for  $C_{19}H_{20}N_2QS$ : 325).

### Example 64

In analogy to example 6 there was prepared on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol with 4-bromobenzonitrile, whereby the product was isolated as free base, 4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-benzonitrile as a white solid. ISP mass spectrum, m/e 330.5 (M+1 calculated for C21F13N3O: 330).

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In analogy to example 6, on reaction of (S) 4 (3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride, product of example 29, with 3-chloromethyl-2-fluoro-pyridine hydrochloride there was obtained: (S) 4-(3-ethoxy-pyrrolidin-1-yl)-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-quinoline hydrochloride as a white solid. ISP mass spectrum, m/e: 382.4 (M+1 calculated for C<sub>22</sub>Fl<sub>24</sub>FN<sub>3</sub>O<sub>2</sub>: 382).

### Transport State of the career result of the Control of the career of the

In analogy to example 6, on reaction of (S)-4\*(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride! product of example 29; with 2-chloro-3-chloromethyl-pyridine hydrochloride there was obtained. (S) 7-(2-chloro-pyridin-3-ylmethoxy)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinoline-hydrochloride as a light yellow-solid. ISP mass spectrum, m/e: 398.4\*(M+1-calculated for C<sub>22</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>25</sub> 398) across the contraction of the contraction o

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In analogy to example 6, on reaction of (S)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride, product of example 29, with 3-chloromethyl-pyridine

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hydrochloride there was obtained: (S) 4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-7-(pyridin-3-ylmethoxy)-quinoline hydrochloride as a light brown solid. ISP mass spectrum, m/e:
364.3 (M+1 calculated for C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>: 364)

### <u>Example 68</u>

In analogy to example 6, on reaction of (S)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol hydrochloride, product of example 29, with 5-chloromethyl-pyridine-2-carbonitrile there was obtained: (S) 5-[4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-pyridine-2-carbonitrile hydrochloride as an off-white solid. ISP mass spectrum, m/e: 389.3 (M+1 calculated for C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: 389).

#### Example 69

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In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-ol-hydrochloride product of example 40, with 3-methoxybenzyl chloride there was obtained: 4-azepan-1-yl-7-(3-methoxy-benzyloxy)=2-methyl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum; m/e: 377.4 (M+1-calculated for C<sub>24</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>-377)

### Example 70

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In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-ol hydrochloride, product of example 40, with 2-bromomethyl-benzonitrile there was obtained: 2-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile hydrochloride as an off-white solid. ISP mass spectrum, m/e: 372.3 (M+1 calculated for C<sub>24</sub>H<sub>25</sub>N<sub>3</sub>O: 372).

### Example 71 and a first first water Example 71 and again the first first for the first firs

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In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-ol hydrochloride, product of example 40, with 3-chlorobenzyl chloride there was obtained: 4-azepan-1-yl-7-(3-chloro-benzyloxy)-2-methyl-quinoline hydrochloride as a light yellow solid ISP mass spectrum, m/e: 3813 (M+1 calculated for C2+H25ClN2O: 381).

In analogy to example 6, on reaction of 4-azepan-1-yl-2-methyl-quinolin-7-ol hydrochloride, product of example 40, with 4-chlorobenzyl chloride there was obtained: 4-Azepan-1-yl-7-(4-chloro-benzyloxy)-2-methyl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 381.3 (M+1 calculated for G<sub>23</sub>H<sub>25</sub>ClN<sub>2</sub>O: 381)

### Example 73

t or one which end for health the best life in the first of A suspension of 98.5 mg (0.25 mmol) of 7-(6-chloro-pyridin-3-ylmethoxy)-2-methyl-4pyrrolidin-1-yl-quinoline hydrochloride, product of example 56, in 0.44 ml (5 mmol) of morpholine was heated under nitrogen at 60% (oil bath temperature) for 23 h and further 72 h at 100°C. The mixture was cooled to RT and partitioned between EtOAc and water. The organic layer was separated washed with water, dried over magnesium acetate and concentrated in vacuo. The residue was taken up in ether (20 ml), insoluble material was removed by filtration and the filtrate treated with 0.1 ml of 3 N HCl in MeOH. The solid that precipitated was collected friturated with ether (5 ml), filtered off by suction, dried in a high vacuum and then applied to a to silica gel column with CH2Cl2/MeOH/NHIOH (19:1: 0.05) as eluent. The purified fractions were combined and concentrated in vacuo to a small volume then acidified by adding a few drops of 3 NHCl in MeOH. The selvent was taken off in vacuo to give 23 mg (18%) of the desired 2-methyl-7-(6-morpholin-4-ylpyridin-3-ylmethoxy)-4-pyrrolidin-1-yl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum; m/e: 405.5 (M+1 calculated for C24FL3NIO2: 405).44 th. 5 mmol of one was deale a unifer alla sern eligit Compacto infaveritie el for the hand weterer

# Example 74 Example 74

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A suspension of 98:5 mg (0:25 mmol) of 7-(6-chiloro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride, product of example 56, 16 mg (0:03 mmol) of BINAP, 2:8 mg (0:01 mmol) of Pd(II) acetate, and 99 mg (1 mmol) of sodium tert-butylate in toluene (4:5 ml) was treated at RT with 36 mg (0:5 minol) of pyrrolidine and then heated at reflux under an argon atmosphere for 4!h. The reaction mixture was cooled to RT, diluted with methylene chiloride (10 ml), and then filtered off by suction and dried in a high vacuum to give 88 mg (84%) of the 2 methyl-4-pyrrolidin-1-yl-7-(6-pyrrolidin-1-yl-pyridin-3-ylmethoxy)-quinoline as a white solid. ISP mass spectrum, m/e: 389:3 (M+1) calculated for C<sub>24</sub>H<sub>28</sub>N<sub>4</sub>O: 389).

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### Example 75

A suspension of 114 mg (0.5 mmol) of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol) product of example 2, 71 mg (0.53 mmol) of 3-dimethylamino-2,2-dimethyl-1-propanol, 196.7 mg (0.75 mmol) of triphenyl phosphine in THF (4 ml) was treated at RT with 123 µl (0.75 mmol) of diethyl azodicarboxylate and stirred at RT for 48 h. The precipitate that had formed was removed by filtration, the filtrate was concentrated in vacuo and the oily residue obtained was applied to silica gel column with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH (90:10: 1) as eluent. The purified fractions were combined and concentrated in vacuo. The residue was taken up in ether, the crystalline solid that formed was filtered off by suction and dried in a high vacuum to give 24 mg (23%) of the desired [2,2-dimethyl-3-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-propyl] dimethyl-amine as an off-white solid. ISP mass spectrum, m/e: 342.4 (M+1 calculated for C<sub>21</sub>H<sub>31</sub>N<sub>3</sub>O: 342). (Further material, 30 mg, 29%, was obtained on concentration of the mother liquid and collection of the product as hydrochloride salt)

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In analogy to example 75, on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, with 4-hydroxy-1-methyl-piperidine there was obtained: 2-methyl-7-(1-methyl-piperidin-4-0-1-yloxy)-4-pyrrolidin-1-yl-quinoline as a yellow solid-ISP mass spectrum, m/e: 326.5 (M+1-calculated for C<sub>20</sub>H<sub>22</sub>N<sub>3</sub>O/326).

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Trum, tole: 542.4 (M+1 calculated for Englished): 341). (Further material, 50 ing.

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In analogy to example 75, on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, with 3-hydroxy-tetrahydrofurane there was obtained 2-methyl-4-pyrrolidin-1-yl-7-(tetrahydrofuran-3-yloxy)-quinoline as a light yellow solid. ISP mass spectrum, m/e: 299.4 (M+1 calculated for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: 299).

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In analogy to example 75, on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, with (1-methyl-piperidin-4-yl)-methanol, and on isolation of the product as hydrochloride,

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there was obtained: 2-Methyl-7-(1-methyl-piperidin-4-ylmethoxy)-4-pyrrolidin-1-yl-quinoline hydrochloride as a white solid. ISP mass spectrum, m/e: 340.3 (M+1 calculated for C<sub>21</sub>H<sub>29</sub>N<sub>3</sub>O: 340).

### Example 79

In analogy to example 75, on reaction of 2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, with 3-morpholin-4-yl-propan-1-ol, and on isolation of the product as hydrochloride, there was obtained: 2-methyl-7-(3-morpholin-4-yl-propoxy)-4-pyrrolidin-1-yl-quinoline hydrochloride as an off-white solid. ISP mass spectrum, m/e: 356.4 (M+1 calculated for C<sub>21</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub>: 356).

# Example 80

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To a cooled (0°C) solution of 2-methyl-4-pyrrolidin-1-yl-quinolm-7-ol (797 mg, 3.49 mmol) in dimethylformamide (13 mL) was added sodium hydride (ca. 60% in oil, 168 mg, 4.19 mmol). After 30 min at 0°C, ethyl bromoacetate (0.5 mL, 4.50 mmol) was injected. After 2h30, an aqueous solution of NaHCO3 was added and the aqueous layer was extracted with dichloromethane. The combined organic phases were washed with brine and water and then dried over sodium sulfate. After filtration, solvents were removed in a high vacuum. The brown oil was triturated with diethylether. After filtration, the solid was dried in a high vacuum to give 660 g (60.2%) of (2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-acetic acid ethyl ester as a light brown solid. ISP mass spectrum, m/e: 315.4 (M+1 calculated for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: 315.4).

# Example 81

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To a cooled (0°C) solution of (2-methyl-4-pyrtolidin-1-yl-quinolin-7-yloxy)-acetic acid ethyl ester (613 mg, 1.95 mmol) in ethyl alcohol (10 mL) was added sodium borohydride (506 mg, 12.84 mmol). The mixture was stirred 7h at room temperature. Aqueous hydrochloride was added carefully (12M; 1 mL). The suspension was filtered and the solid was washed with MeOH. The solution was dried over sodium sulfate, filtered and the solvent was removed in a high vacuum to give 425 mg (80.0%) of 2-(2-methyl-4-1-) pyrrolidin-1-yl-quinolin-7-yloxy) ethanol as a brown-oil-1SP mass spectrum, m/e: 273.4 (M+1 calculated for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>: 273.4).

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### Example 82

To a cooled (0°C) solution of of 2-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxy)-ethanol (425 mg, 1.56 mmol) in dichloromethane (20 mL) was added triethylamine (0.9 mL, 6.49 mmol) and tosyl chloride (1115 mg, 5.85 mmol). The reaction mixture was stirred 22 h at room temperature. An aqueous solution of NaHCO3 was added. After separation, the organic layer was washed with brine. The brown gum was triturated with diethylether. After filtration, the solid was dried in a high vacuum to give 520 mg (78.1%) of toluene-4-sulfonic acid 2-(2-methyl-4-pyrrolidin-1-yl-quinolîn-7-yloxy)-ethyl ester as a light yellow solid. ISP mass spectrum, m/e: 427.5 (M+1 calculated for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>S: 427.5).

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In analogy to example 6 there was prepared: on reaction of 2-methyl-4-pyrrolidin-T-yl-nol quinolin-7-ol with 1-(2-pyridyl)-3-chloropropane, there was obtained: 2'methyl-7-(3-4-pyridin-2-yl-propoxy): 4-pyrrolidin-1-yl-quinoline as a yellow viscous oil: ISP mass - spectrum, in/e348.5 (M+1-calculated for C<sub>22</sub>H<sub>32</sub>N<sub>3</sub>O 348.5)] and the spectrum of the

## Example 84 solid [52] mass spectrum takes 127. The foreign solid [53] mass spectrum takes 127. The foreign solid [53] mass spectrum takes 127. The foreign solid [53] mass spectrum takes 127. The foreign solid [54] mass spectrum takes 127. The foreign spectrum takes 127. The foreign solid [54] mass spectrum takes 127

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In analogy to example 1, on reaction of 7-benzyloxy-4-chloro-2-methyl-quinoline with morpholine, there was obtained: 7-benzyloxy-2-methyl-4-morpholin-4-yl-quinoline as a waxy yellow solid. ISP mass spectrum, m/e-335.3 (M+1 calculated for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: 335).

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In analogy to example 1, on reaction of 7-benzyloxy-4-chloro-2-methyl-quinoline, with an excess of (S)-3-hydroxypyrrolidine (2,5 mole-equivalents) in 1-methyl-2-pyrrolidone as solvent at 100°C, there was obtained: (S)-1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-3-ol as a light brown solid. ISP mass spectrum, m/e: 335.4 (M+1 calculated for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: 335).

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### Example 86

In analogy to example 1, on reaction of 7-benzyloxy-4-chloro-2-methyl-quinoline, with an excess of (R)-3-hydroxypyrrolidine (2,5 mole-equivalents) in 1-methyl-2-pyrrolidone as solvent at 100°C, there was obtained: (R)-1-(7-benzyloxy-2-methyl-quinolin-4-yl)pyrrolidin-3-ol as a light brown solid. ISP mass spectrum, m/e: 335.3 (M+1 calculated for C21H22N2O2: 335). Tall The Chronics of the Self 18 of the Wall Self Chronic Self the Self the thorn to be careen

### Example 87. Land And Andrew Example 87.

AND THE RESIDENCE OF THE PARTY In analogy to example 1, on reaction of 7-benzyloxy-4-chloro-2-methyl-quinoline, with an excess of (S)-2-(hydroxymethyl)pyrrolidine (2,5 mole-equivalents) in 1-methyl-2pyrrolidone as solvent at 100°C, there was obtained: (S)-[1-(7-benzyloxy-2-methylquinolin-4-yl)-pyrrolidin-2-yl]-methanol as an off-white solid. ISP mass spectrum, m/e: 349.5 (M+1 calculated for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: 349) white we example to an Testing of Testing of The probable and the probable of the control of the excuse of the -2-hvarpaying colleges 12. Turnes is twivelents but 1-methyl-2-pygrolidane as

### waven of 100 %, overs was obtained to 141-17-henry and Arasin clin-4-vi)private les colons ally at the south to the Example 88 rate and the colon of the legislation for The second secon

In analogy to example 1, on reaction of 7-benzyloxy-4-chloro-2-methyl-quinoline, with an excess of (S)-2-(methoxymethyl)pyrrolidine (2,5 mole-equivalents) in 1-methyl-2pyrrolidone as solvent at 100°C, there was obtained: (S)-7-benzyloxy-4-(2methoxymethyl-pyrrolidin I yl) 2 methyl-quinoline as an orange viscous oil ISP mass spectrum, m/e: 363-2 (M+1-calculated for C23H26N2O2: 363). portoligone exactivent et tippe forme was obtained (Sp. (1-17-ben of oxy-2-methy);

# tatory of containing factors of Example 89 and but on the many of the an

consoln-4-si opyr olidlu-2-yil megozul-14-lide while while solid 159 mass specifium, mes

In analogy to example 2, on hydrogenation of (\$)-7-benzyloxy-4-(2-methoxymethylpyrrolidin-1-yl)-2-methyl-quinoline, product of example 88, with Pd on charcoal (10%) in MeOH, there was obtained: (S)-4-(2-Methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol as a yellow solid ISP mass spectrum; m/e: 273.2 (M+1 calculated for  $C_{16}H_{20}N_{2}O_{2}$ : and the state of t 

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The state of the s In analogy to example 6, on reaction of (S)-4-(2-Methoxymethyl-pyrrolidin-1-yl)-2methyl-quinolin-7-ol, product of example 89, with 2-chloro-3-chloromethyl-pyridine hydrochloride there was obtained: (S)-7-(2-chloro-pyridin-3-ylmethoxy)-4-(2-30

methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 398.4 (M+1 calculated for C<sub>22</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>2</sub>: 398).

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In analogy to example 6, on reaction of (S)-4-(2-Methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 89, with 2-fluoro-3-chloromethyl-pyridine hydrochloride there was obtained: (S)-7-(2-fluoro-pyridin-3-ylmethoxy)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 382.4 (M+1 calculated for C<sub>22</sub>H<sub>24</sub>FN<sub>3</sub>O<sub>2</sub>: 382).

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In analogy to example 6, on reaction of (S)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 89, with cyclopropylmethyl bromide hydrochloride there was obtained: (S)-7-cyclopropylmethoxy-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinoline hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 327;4 (M+1 calculated for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>: 327)

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In analogy to example 2, on hydrogenation of (S)-[1-(7-benzyloxy-2-methyl-quinolin-4-yl)-pyrrolidin-2-yl]-methanol, product of example 87, with Pd on charcoal (10%) in MeOH, there was obtained: (S)-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol as a yellow solid. ISP mass spectrum; m/e: 259.3 (M+1 calculated for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>: 259).

## Example 94: Supering the production of the Example 94: Supering the production of the Example 94:

In analogy to example 6, on reaction of (S)-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 93, with 2-fluoro-3-chloromethyl-pyridine hydrochloride there was obtained: (S)- {1-[7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-quinolin-4-yl]-pyrrolidin-2-yl}-methanol as a light yellow solid; ISP mass spectrum, m/e: 368.4 (M+1 calculated:for C2:H2:FN3O2: 368).

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#### Example 95

In analogy to example 6, on reaction of (S)-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2 methyl-quinolin-7-ol, product of example 93, with 2-chloro-3-chloromethyl-pyridine hydrochloride there was obtained: (S)- {1-[7-(2-chloro-pyridin-3-ylmethoxy)-2-methyl-quinolin-4-yl]-pyrrolidin-2-yl}-methanol as a light yellow solid. ISP mass spectrum; m/e: 384.3 M+1 calculated for C<sub>21</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>2</sub>: 384).

### Example:96

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In analogy to example 6, on reaction of (S)-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 93, with 2-bromomethyl-benzonitrile there was obtained: (S)-2-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile as an offi-white solid-ISP mass spectrum, in/e: 374:5 (M+1 calculated for C<sub>23</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>: 374)

# Example 97 The First Constitution of the fir

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In analogy to example 6, on reaction of (S)-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 93, with 3-chlorimethyl-pyrrolidin there was obtained: (S)- {1-[2-methyl-7-(pyridin-3-ylmethoxy)-quinolin-4-yl]-pyrrolidin-2-yl}-methanol as an light yellow solid. ISP mass spectrum m/e: 350.5 (M+1) calculated for C<sub>21</sub>H<sub>22</sub>N<sub>3</sub>O<sub>2</sub>: 350).

### Example 98

In analogy to example 6, on reaction of (S)-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol, product of example 93, with 5-chloromethyl-pyridin-2-carbonitrile there was obtained: (S)-5-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-pyridine-2-carbonitrile as an light yellow solid: ISP mass spectrum, m/e: 375.3 (M+T-calculated for C<sub>22</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub>: 375).

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a) A mixture of 3.1 g of (10.9 mmol) of 7-benzyloxy-4-chloro-6-fluoro-2-methylquinoline and 18.1 ml-(21.8 mmol) pyrrolidine was heated at 80°C (oil bath temperature) under an argon atmosphere for 6 h. The reaction mixture was concentrated in vacuo, the residue taken up in methylene chloride, which was washed with water, saturated NaCl solution and then dried over magnesium sulphate. The solvent was removed in vacuo, the residue purified by flash chromatography on silica gel with CH<sub>2</sub>Cl<sub>2</sub>/MeOH (100:0 to 90:10 over 1 h) as eluent. Combination of the purified fractions and concentration in vacuo gave 1.7 g (46.2%) of the 7-benzyloxy-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline as a brown crystalline solid. ISP mass spectrum, m/e: 337.4 (M+1 calculated for C<sub>21</sub>H<sub>21</sub>FN<sub>2</sub>O: 337).

# Preparation of the starting material:

c) 79 g (0.62 mol) of 4-fluoro-3-hydroxy-aniline in DMF (1.31) were treated under argon portionwise over a period of 15 minutes with 76.7 g (0.68 mol) of potassium t-butylate whereas the temperature of the reaction solution was kept between RT and 28°C. Stirring was continued for 15 minutes then 79 ml (0.68 mol) of benzyl chloride were added dropwise while keeping the temperature of the reaction solution between RT and 30°C. After stirring for 2 h at RT the reaction solution was poured into ice water (61) which was then extracted 3-fold with ether (about 31 each). The combined organic layers were washed with brine (1.51) and dried over magnesium sulfate and the solvent removed in vacuo. The residue was purified by chromatography over a short silica gel column with

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methylene chloride as eluent. Combination of the purified fractions and concentration in vacuo gave 92.7 g (68.6%) of the desired 3-benzyloxy-4-fluoro-phenylamine as light yellow crystalline solid. ISP mass spectrum, m/e: 218.2 (M+1 calculated for C<sub>13</sub>H<sub>12</sub>FNO: 218.2).

- c) 92.7 g (0.43 mol) of 3-Benzyloxy-4-fluoro-phenylamine, 57 ml (0.45 mol) of ethyl acetoacetate and 0.81 g (4 mmol) of p-toluenesulfonic acid monohydrate in 370 ml of cyclohexane were heated at reflux for 3 h in the presence of a water separator funnel. The reaction mixture was cooled to RT, ACOEt (11) and saturated aqueous NaHCO<sub>3</sub> solution (0,5 l) were added, the layers were separated and the organic layer once extracted with AcOEt (0.3 l). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo to give 140 g (100%) of the desired 3-(3-benzyloxy-4-fluoro-phenylamino)-but-2-enoic acid ethyl ester as yellow-orange crystalline solid. Melting point: 79°C-80°C.
- d) 70:35 g (0:21 mol) of 3-(3-benzyloxy-4-fluoro-phenylamino)-but-2-enoic acid ethyl ester in Dowtherm A (220 ml) were added dropwise under argon to 400 ml of Dowtherm

  A heated at 250°C (metal bath temperature). The solution was stirred further 15 minutes at 250°C (bath temperature), cooled to RT and n-hexane was added with stirring whereby a light brown solid formed that was collected by filtration and washed with 4-times with n-hexane. The solid was then triturated with ether, collected by suction, washed 3-times with ether and then dried in a high vacuum, to give 33.9 g (57%) of the desired7-benzyloxy-6
  fluoro-2-methyl-1H-quinolin-4-one as a light brown solid. ISP mass spectrum, m/e: 284.1 (M+1 calculated for C<sub>17</sub>H<sub>14</sub>FNO<sub>2</sub>: 284).
- e) 67.8 g (0.239 mol) of 7-benzyloxy-6-fluoro-2-methyl-1H-quinolin-4-one in 220ml (2.39 mol) of POCl<sub>3</sub> were heated at reflux for 90 minutes. The reaction mixture was cooled to RT and the solvent was removed in vacuo. The residue was partitioned between ice water (1.5.1) and methylene chloride (1.1), and 250 ml of concentrated ammonia were added slowly with stirring to adjust the aqueous layer to pH9. The layers were separated, the aqueous layer twice extracted with methylene chloride (each 500 ml), the combined organic layers were washed with brine dried over magnesium sulfate and then concentrated in vacuo, to give 71.5 g (86.83%) of the desired of 7-benzyloxy-4 chloro-6-fluoro-2-methyl-quinoline as an off white solid. Melting point: 110°C-111°C.

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### Example 100

A solution of 1:5 g (4:46 mmol) of 7-benzyloxy-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline, product of example 99, dissolved in 40 ml of MeOH was treated with 0.375 g of palladium on charcoal (10%) and then hydrogenated at RT for 1:5 h until HPLG analysis indicated the completion of the reaction. The catalyst was filtered off, and the solution was concentrated in vacuo. The residue was triturated with AcOEt, collected by filtration and dried in a high vacuum to give 1.02 g (92.8%) 6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol as an yellow solid. ISP mass spectrum, m/e: 247.3 (M+1 calculated for C<sub>14</sub>H<sub>15</sub>FN<sub>2</sub>O: 247).

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### Example 101

In analogy to example 6 there was prepared: on reaction of 6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 100-with 4-bromomethyl-benzonitrile whereby the product was isolated as free base, 4-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile as an off-white solid. ISP mass spectrum, m/e: 362.2(M+1 calculated for Ca-H<sub>20</sub>FN<sub>3</sub>O: 362).

#### Example 102

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Example 1

In analogy to example 6 there was prepared: on reaction of 6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-ol, product of example 100, with 3-chloromethyl 2-fluoro-pyridine hydrochloride whereby the product was isolated as free base, 6-fluoro-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline as an brown solid. ISP mass spectrum, m/e: 356.4 (M+1 calculated for C20H19F2N3O: 356) as perturbatives.

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In analogy to example 6 there was prepared; on reaction of 6-fluoro-2-methyl-4pyrrolidin-1-yl-quinolin-7-ol, product of example 100, with 2-chloro-3-chloromethyl pyridine hydrochloride whereby the product was isolated as free base, 7-(2-chloropyridin-3-ylmethoxy)-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline as a light brown solid. ISP mass spectrum, m/e: 372.3 (M+1-calculated for C<sub>20</sub>H<sub>19</sub>ClFN<sub>3</sub>O: 372)

### Bxample 105

In analogy to example 6 there was prepared: on reaction of 6-fluoro-2-methyl-4pyrrolidin-1-yl-quinolin-7-ol, product of example 100, with 3-chloromethyl-2-methylpyridine hydrochloride whereby the product was isolated as free base; 6-fluoro-2-methyl-7-(2-methyl-pyridin-3-ylmethöxý). 4-pyrrolidin-1-yl-quinoline an light yellow solid. ISP mass spectrum, m/e: 352.4(M+1) calculated for C21H22FN3O: 352).05 - 12th or one critical cone hydrocial sends whereby the province was noticed as free case. The horizon as a ship of the control of the

In analogy to example 6 there was prepared: on reaction of 6-fluoro-2-methyl-4pyrrolidin-1-yl-quinolin-7-ol, product of example 100, with 3-chloromethyl benzonitrile whereby the product was isolated as free base, 3-(6-fluoro-2-methyl-4-pyrrolidin-1-ylquinolin-7-yloxymethyl) benzomtrile as an off-white solid. ISP mass-spectrum, m/e. - -- - - Fore door de gierer grodie was in 1965 is beer biske of his being and the

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In analogy to example 6 there was prepared, on reaction of 6-fluoro-2-methyl-4pyrrolidin-1-yl-quinolin-7-of, product of example 100, with 2-bromomethyl benzonitrile whereby the product was isolated as free base, 2-(6-fluoro-2-methyl-4-pyrrolidin-1-ylquinolin-7-yloxymethyl) benzonitrile as light brown solid. ISP mass spectrum, m/e: 362.2(M+1 calculated for C22H20FN30:1362)

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#### Example 108

In analogy to example 6 there was prepared: on reaction of 6-fluoro-2-methyl-4pyrrolidin-1-yl-quinolin-7-ol; product of example 100, with cyclopropylmethyl bromide, 7-cyclopropylmethoxy-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline hydrochloride as a yellow solid. ISP mass spectrum, m/e: 301.3(M+1 calculated for C18H21FN2O: 301).

### Example 109

निर्मात प्राम्पान करता स्थापन प्रमुक्ति के विवास का विकास करता के सम्मान करता है। यह स्थापन के स्थापन के स्थापन 

In analogy to example 6 there was prepared: on reaction of 6-fluoro-2-methyl-4pyrrolidin-1-yl-quinolin-7-ol, product of example 100, with 5-chloromethyl-pyridine-2carbonitrile, whereby the product was isolated as free base, 5-(6-fluoro-2-methyl-4pyrrolidin-1-yl-quinolin-7-yloxymethyl)-pyridine-2-carbonitrile as light grey solid. ISP mass spectrum, m/e 363.2(M+P calculated for C21H16FN4O: 363):0-2-128.4-4v remain-i-M-get religies-offentaduct of exemple 100, with the property inether brancide.

Suspension of 3.2 g (9.5 mg/s) completes the visite of the control A suspension of 3.2 g (9.5 mmol) of (R)-1-(7-benzyloxy-2-methyl-quinolin-4-yl)pyrrolidin-3-ol, product of example 86, in THF (275 ml) was treated at RT under nitrogen with 1.42 g (12.4 mmol) of potassium tert-butoxide. The suspension was stirred for 20 minutes at RT-then 0.72 ml (11.4 mmol) of methyl iodide were added. After 25 minutes of stirring further 0.284 g (2.48 inmol) of potassium tert butoxide were added followed by 0.144 ml (2.28 mol) of methyl lodide (10 minutes later) for completion of the reaction. Stirring was confinued for 20 minutes, the reaction mixture was then concentrated in vacuo and the residue partitioned between water and AcOEt. The layers were separated the aqueous layer once extracted with AcOEt, the combined organic layers washed with brine, dried over magnesium sulphate and concentrated in vacuo to give 3.33 g (94.5%) (R)-7-benzyloxy-4-(3-methoxy-pyrrolidin=1=yl)-2=methyl-quinoline as an orange viscous oil. ISP mass spectrum, m/e: 349.5 (M+1 calculated for C22H24FN2O2: 349).

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In analogy to example 110 there was prepared on reaction of (S)-1-(7) benzyloxy 2-7 methyl-quinolin-4-yl) pyrrolidin-3-ol, product of example 85 with 2-bromoethyl methyl

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ether, (S)-7-benzyloxy-4-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinoline an orange viscous oil. ISP mass spectrum, m/e: 393:4(M+1 calculated for C24H28N2O3: 393). 2000年1月1日中央1月1日的市场上海中央1月1日中国市场中国市场中国市场中国市场中国市场中国市场中国市场的市场中国市场的市场。

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In analogy to example 110 there was prepared; on reaction of (S)-1-(7-benzyloxy-2methyl-quinolin-4-yl)-pyrrolidin-3-ol, product of example 85, with methyl iodide, (S)-7benzyloxy-4-(3-methoxy-pyrrollidin-1-yl)-2-methyl-quinoline as an yellow viscous oil. ISP mass spectrum, m/e: 349:3 (M+1-calculated for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: 349):

In analogy to example T10 there was prepared: on reaction of (S)-1-(7-benzyloxy-2methyl-quinolin-4-yl)-pyrrolidin-3-ol, product of example 85, with cyclopropyl bromide, (S)-7-benzyloxy-4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-2-methyl-quinoline as an orange viscous oil. ISP mass spectrum, m/e: 389.2 (M+1 calculated for C25H28N2O2: 389). grand and a think his broken will be a company of the material of the first of the his hard and the

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### Example 114

न्त्र कार्याचारा हो स्थान स्थान स्थान होते हैं के लिए होते हैं है जिसके हैं के स्थान के लिए हैं के लिए हैं के

In analogy to example 110 there was prepared: on reaction of (S)-1-(7-benzyloxy-2methyl-quinolin-4-yl)-pyrrolidin-3-ol, product of example 85, with toluene-4-sulfonic acid 3-methoxy-propyl ester, (S)-7-benzyloxy-4-[3-(3-methoxy-propoxy)-pyrrolidin-1yl]-2-methyl-quinoline as an yellow viscous oil. ISP mass spectrum, m/e: 407.3 (M+1 calculated for C25H30N2O4: 407). the first first the first with the content of the first specific with contour by the contest of the contest of

### รับการเกลา และสามาร์สามาร์สามาร์สามาร์สามาร์สามาร์สามาร์สามาร์สามาร์สามาร์สามาร์สามาร์สามาร์สามาร์สามาร์สามาร์ Example 115

In analogy to example 110 there was prepared: on reaction of (S)-1-(7-benzyloxy-2methyl-quinolin-4-yl)-pyrrolidin-3-ol, product of example 85, with 2-(2-bromo-ethoxy)tetrahydro-pyran, 7-benzyloxy-2-methyl-4-[(3S)-3-[2-(tetrahydro-pyran-2-yloxy)ethoxy pyrrolidin I-yll quinoline as an yellow viscous oil. ISP mass spectrum, m/e: 363.4 (MFT calculated for Cz.H31N204: 463). Product at element with reluence 4. sulform.

#### Example 116

In analogy to example 2, on hydrogenation of (S)-7-benzyloxy-4-[3-(2-methoxy-ethoxy)pyrrolidin-1-yl]-2-methyl-quinoline, product of example 111, with Pd on charcoal (10%). in MeOH, there was obtained: (S)-4-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-2-methylquinolin-7-ol as a yellow solid. ISP mass spectrum, m/e: 303.4 (M+1 calculated for C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: 303).

### The conference of the conferen The LANGE CAN AND THE RESERVE OF Example 117 or 1481 Enter Can Arrelley, The

In analogy to example 2, on hydrogenation of (S)-7-benzyloxy-4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinoline, product of example 112, with Pd on charcoal (10%) in MeOH, there was obtained: (S)- 4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol as a yellow solid. ISP mass spectrum, m/e: 259.2 (M+1 calculated for CisH<sub>18</sub>N<sub>2</sub>O<sub>2</sub>: 259)<sup>11</sup> in bieCiti. Alectivas pagingas (Sig trija-12-militogy-othroming reprintition-trija-banemuroutnoim-Tul at a velicit volid. 187, confermental Example 118

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In analogy to example 2, on hydrogenation of (S)-7-benzyloxy-4-(3-cyclopropylmethoxypyrrolidin-1-yl)-2-methyl-quinoline, product of example 113, with Pd on charcoal (10%) in MeOH, there was obtained: (S)-4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-2-methylquinolin-7-ol as a yellow solid. ISP mass spectrum, m/e: 299.3 (M+1 calculated for G18H-2N2O2 299) 10-2 2. on hydrug nation of (5)-7-benzydovy 4-(2-mgth 26)-pystokain-1-vi. I-memy-quir gline irroduct et etappie (1) keiliëd of inustical (100 in MeCid.

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# Example 119

In analogy to example 2, on hydrogenation of (S)-7-benzyloxy-4-[3-(3-methoxypropoxy)-pyrrolidin-1-yl]-2-methyl-quinoline, product of example 114, with Pd on charcoal. (10%) in MeOH, there was obtained: (S)- 4-[3-(3-methoxy-propoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-ol as a yellow solid ISP mass spectrum, m/e 317 (M+4) calculated for CisH21N2O3: 317) Fire prochain a service Library Polyage and Aller in Market designed of the property of the prop

## Example 120

In analogy to example 2, on hydrogenation of 7-benzyloxy-2-methyl-4-((3S)-3-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-pyrrolidin-1-yl}-quinoline, product of example 115,

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with Pd on charcoal (10%) in MeOH, there was obtained: 2-methyl-4-{(3S)-3-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-pyrrolidin-1-yl}-quinolin-7-ol as a yellow solid. ISP mass spectrum, m/e: 373.4.3 (M+1 calculated for  $C_{21}H_{28}N_2O_4$ : 373). ार प्रकृतिक के अन्य विकार के प्रकृतिकाल के किया व्यवसाधित के विकार के लिए के किया है।

In analogy to example 6, on reaction of (S) 4-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-2methyl-quinolin-7-ol, product of example 116, with 4-bromomethyl benzonitrile there was obtained: (S)- 4-{4-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7yloxymethyl)-benzonitrile hydrochloride as a light yellow solid. ISP mass spectrum, m/e: 418.4 (M+1 calculated for C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>: 418.4). 418.4 (M+1 calculated to C25.427.5000 in Medit, to see that obtained I methyl-1 (55) 5-12-12 (M+1 calculated to C25.427.500 in Medit, to see that of an amount 7, of as a yellow solid. ISP to see that, m/1 575 13 (At+1 calculated to C25.42.500) in Medit, to see that of the calculated to C25.42.500 in Medit, and the calculated

In analogy to example 6, on reaction of (S)-4-(3-methoxy-pyrrolidin-1-yl)-2-methylquinolin-7-ol, product of example 117, with 4-bromomethyl benzonitrile there was obtained: (S)-4-[4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]benzonitrile hydrochloride as a light yellow solid. ISP mass spectrum, in/e: 374.4 (M+1 calculated for C23H23N3O2-374). 

### 3.4 (Al-) calculated to Castle NOS

In analogy to example 6, on reaction of (S)-4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-2-20 methyl-quinolin-7-ol, product of example 1.18, with 4-bromomethyl benzonitrile there was obtained: (S)-4-[4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7yloxymethyl]-benzonitrile hydrochloride as an off white solid. TSP mass spectrum, m/e: 

### the first of the fight of the first of the f Example 124

In analogy to example 6, on reaction of (S)- 4-[3-(3-methoxy-propoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-Z-ol, product of example 119, with 4-bromomethyl benzonitrile there was obtained: (S)-4-{4-[3-(3-methoxy-propoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7yloxymethyll-benzonitrile hydrochloride as an off-white solid. ISP mass spectrum, m/e: 432.5 (M+1 calculated for G26H29N3O3 432)-r

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In analogy to example 6, on reaction of 2-methyl-4-(3S) 3-[2-(tetrahydro-pyran-2yloxy)-ethoxyl-pyrrolidin-1-yl}-quinolin-7-ol, product of example 120, with 4bromomethyl benzonitrile, and subsequent cleavage of the THP ether protecting group whereby the product was isolated as free base, there was obtained: (S)-4-{4-[3-(2-11.00)] Hydroxy-ethoxy)-pyrrolidin-1-yl]-2-methyl-quinolin-7-yloxymethyl}-benzonitrile as a white yellow solid. ISP mass spectrum, m/e: 405.3 (M+1 calculated for  $C_{24}H_{25}N_3O_3$ : 403).

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In analogy to example 99, on reaction of 7-benzyloxy-4-chloro-6-fluoro-2-methylquinoline, with an excess of (S)-2-(hydroxymethyl)pyrrolidine (2,5 mole-equivalents) in 1-methyl-2 pyrrolidone as solvent at 100°C; there was obtained (S) 111 (7 benzyloxy 6 fluoro 2 methyl-quinolin-1-yl) pyrrolidin-2-yl) methanol as an light brown solid. ISP mass speetrum m/e:36743 (M+1 calculated for C2H2PN2O2-367)) er protecting group 

In analogy to example 100, on hydrogenation of (S)-[1-(7-benzyloxy-6-fluoro-2-methylquinolin-4-yl)-pyrrolidin-2-yl]-methanol, product of example 126, with Pd on charcoal (10%) in MeOH, there was obtained: (S)-6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-ol as a light brown solid ISP mass spectrum, m/e: 277:3 (M+1 calculated for Cista:FN:05:12773; which the bottom in the commission of the commissi

Example 128 In analogy to example 6, on reaction of (S)-6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-25 yl)-2-methyl-quinolin-7-ol, product of example 127, with 4-bromomethyl benzonitrile, whereby the product was isolated as free base, there was obtained: (S)-4-[6-fluoro-4-(2hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzomtrile as an light grey solid, ISP mass spectrum; m/e-392.3 (M+1 calculated for C25H22FN3O2 392)

#### Example 129 and all tripped to

In analogy to example 6, on reaction of (S)-6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1vl)-2-methyl-quinolin-7-ol, product of example 127, with 5-chloromethyl-pyridine-2carbonitrile, whereby the product was isolated as free base, there was obtained: (S)-5-[6fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-pyridine-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxymethyl-pyrrolidin-1-yloxyme2-carbonitrile as a grey solid. ISP mass spectrum, m/e: 393.3 (M+1 calculated for C22H21FNaO2: 393) Example 130

a) A solution of 1.42 g of (4.6 mmol) of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-10 benzonitrile and 1.11 g (12.5 mmol) of (S)-3-hydroxypyrrolidine in 1-methyl-2pyrrolidine (25 ml) was heated under nitrogeniat 100°C (oil bath temperature) for 23-h. The reaction mixture was concentrated in a high vacuum, the residue taken up in methylene chloride, which was washed with water, saturated NaCl solution and then dried over magnesium sulphate. The solvent was removed in vacuo, the residue triturated with  $1\tilde{5}$ MeOH, filtered off by suction, washed subsequently with MeOH and ether and then dried in a high vaccum to give 1.45 g (83.86%) of the (S) 4-[4-(3-hydroxy-pyrrolidin-1-yl)-2methyl-quinolin-7-yloxymethyl]-benzonitrile as a brown solid. ISP mass spectrum, m/e: 360.2 (M+1 calculated for  $C_{22}H_{21}N_3O_2$ : 360.2),

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transkom en Literauska kompetation kalida politica politica politica i politica politica politica politica pol b) A solution of 3 g (10.5 mmol) of 7-benzyloxy-2-methyl-quinolin-4-ol product of example 1 c), dissolved in 270 ml of MeOH was treated with 1 g of palladium on charcoal. (10%) and then hydrogenated at RT for 1 h until HPLC analysis indicated the completion of the reaction. The catalyst-was filtered off, washed with MeOH, and the solution was concentrated in vacuo. The residue was triturated with ether, collected by filtration and dried in a high vacuum to give 2.05 g (98.6%) 2-methyl-quinoline-4,7-diol as an off-white solid. ISP mass spectrum, m/e: 176.2 (M+1 calculated for C<sub>10</sub>H<sub>9</sub>NO<sub>2</sub>: 176).

c) A mixture of 2.05 g (10.4 mmol) of 2-methyl-quinoline-4,7-diol, 1.72 g (12.5 mmol) of <u>ن</u>. potassium carbonate and 2.1 g (12.5 mmol) of 4 (bromomethyl) benzonitrile in 100ml of 30 DMF were stirred at RT under an nitrogen atmosphere for 4 h until completion of the reaction according to HPLC analysis. The reaction mixture was cooled to RT and poured

into EtOAc / water (300 ml./ 400 ml.) The product that precipitated was filtered off by suction, washed with water AcOEt and ether and dried in a high vacuum to give 2-23 g. (73%) of 4 (4-hydroxy-2-methyl-quinolin-7-yloxymethyl)-benzonitrile as a white solid. ISP mass spectrum, m/e: 291.4 (M+1 calculated for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>: 291).

d) 2.22 g (7.6 mmol) of 4-(4-hydroxy-2-methyl-quinolin-7-yloxymethyl)-benzonitrile in 14.2 ml (151.7mmol) of POCl<sub>3</sub> were heated at 130°C (oil bath-temperature) for 1h 50 min until completion of the reaction according to TLC analysis. The reaction mixture was cooled to RT and the solvent was removed in vacuo. The residue was taken up in ice water and stirred for 15 minutes. The pH was adjusted to values between pH 9-10 with inconcentrated NH<sub>2</sub>OH an stirring was continued for 2h. The brown solid, which precipitated was filtered off by suction, washed with water and subsequently dried in a high vacuum. This gave 2.38 g (100%) of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile as a yellow solid. ISP mass spectrum, m/e: 209 (M+1 calculated for C<sub>18</sub>H<sub>13</sub>ClN2O: 309).

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In analogy to example 130 on reaction of 4 (4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R)-3-hydroxypyrrolidine, there was obtained (R)-4-[4-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile as a brown solid. ISP mass spectrum, m/e 360.3 (M+1 calculated for C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub> 360).

#### Example 132

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R,S)-2-methylpyrrolidine, there was obtained (R,S)-4-[2-methyl-4-(2-methyl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile as a beige solid TSP mass spectrum, m/e/358.2 (M+1 calculated for C23H23N3O: 358)

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In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)benzonitrile, product of example 130 d); with (S)-2-(hydroxymethyl)pyrrolidine, there

was obtained: (S)-4-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7yloxymethyl]-benzonitrile as a light yellow solid. ISP mass spectrum, m/e: 374.4 (M+1 calculated for C23H23N3O2f374) action of the control of the contro the executional proportion of society as a second section of the second section of the second section of the second

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# Example 135

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trains which distings a countrie the analysis and in a prepare of the interpretation In analogy to example 130, on reaction of 4-(4-chlore-2-methyl-quinolin-7-yloxymethyl)benzonitrile, product of example 130 d), with (R)-3- (dimethylamino)pyrrolidine, there was obtained: (R)-4-[4-(3-dimethylamino-pyrrolidin-1-yl)-2-methyl-quinolin-7yloxymethyl]-benzonitrile as a light brown solid. ISP mass spectrum, m/e. 387.3 (M+1) calculated for C2H26N4O:387914 100 de vitto En They decidence for more outline. There र तर र अन्य स्थापित स्

## INSTALL TO CONTRACT SELECTION VENEZAS Example 136

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-20 benzonitrile, product of example 130 d), with (S)-3-(dimethylamino)pyrrolidine, there was obtained: (S)-4-[4-(3-dimethylamino-pyrrolidin-1-yl)-2-methyl-quinolin-7yloxymethyl] benzonitrile as a light brown solid. ISP mass spectrum; m/e. 387/3 (M/+1) calculated for C2H2N1O:387) 在"大学的特别"的一种企业的开展的中国的特殊的

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## 1、1500年的支持中央,在中国大学中的大学中的大学中的大学中的大学中国大学中国大学中国大学中国大学中国大学中国 Example 137

In analogy to example 130, on reaction of 42(4-chloro-2-methyl-quinolin-7-yloxymethyl)benzonitrile, product of example 130 d), with (R)-2-(methoxymethyl)pyrrolidine, there was obtained: (R)-4-[4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7yloxymethyl]-benzonitrile as a light brown solid. ISP mass spectrum, m/e: 388.3 (M+T) calculated for C2H75N3O2 388).

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)benzonitrile, product of example 130 d), with (S)-2-(methoxymethyl)pyrrolidine, there was obtained: (S)-4-[4-(2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7yloxymethyl]-benzonitrile as a light brown solid ISP mass spectrum, m/e: 388.3 (M+1 calculated for C<sub>24</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>: 388) The Table of the control of the cont

## 了一个大型,可以为1994年,1994年,1995年,1995年,1995年,1995年,1995年,1995年,1995年,1995年,1995年,1995年,1995年,1995年,1995年,1995年,1995年 That we have the state of the state of the Example 139 and the state of the state o

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In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-10 benzonitrile, product of example 130 d), with (R,S)-2-isopropyl-pyrrolidine, there was obtained: (R,S)-4-[4-(2-isopropyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]benzonitfile hydrochloride as a light yellow solid ISP mass spectrum, m/e: 386.4 (M+1) calculated for C25H27N3O 3869 110 d. with S. 2 fraction symmetry, perceliding there was obtained (5)-4-4 (2-dictoroned of the dien -- Vi-1 medity-quincing) Ξ

## Example 140

"The methyl - tenzoniu as us a Bent programming 127 mass spectrum inter 578 2 (M-1

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)benzonitrile, product of example 130 d), with (S)-proline methyl ester, there was obtained: (\$)-1-[7-(4-cyano-benzyloxy)-2-methyl-quinolin-4-yl]-pyrrolidine-2-carboxylic acid methyl ester as a white solid ISP mass spectrum; m/e: 402.5 (M#1 calculated for C24H23N3O3: 402) just of exemple 130 di Wittill 200 Lisopropol pyrolium, there was entined. Si--- isomory-minimin-i-vi-- the invitation via valency राज्यात्राचा र मेरबार मार्ग्यात्रात्रात्रा के विकास स्थापिक स्थापिक स्थापिक स्थापिक स्थापिक स्थापिक स्थापिक स् e adaleste les l'appendent de de la lance de la latinoximient de latinoximient de la latinoximient de la latinoximient de la latinoximient de la latinoximient de latinoximient de la latinoximient de latinoximient de latinoximient de la latinoximient de latinoximient de la latinoximient de latinoxim 41 Depth Ten February Screen works 14 Depth 2 District Constitution of the Constituti

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)benzonitrile, product of example 130 d), with (R)-3-(methylamino)pyrrolidine there was 25 obtained: (R)-4-[2-methyl-4-(3-methylamino-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]benzonitrīle as a yellow foam. ISP-mass spectrum: m/e: 373:4 (M+1 calculated for C23H24N4O: 373)

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### Example 142

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)benzonitrile, product of example 130 d), with (S)-3-(methylamino)pyrrolidine there was obtained: (S)- 4-[2-methyl-4-(3-methylamino-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]benzonitrile as a brown foam. ISP mass spectrum, m/e: 373.4 (M+1 calculated for i juli likytter fekkiri fikkejelektijehe 2. metji-- juhildin-te juhan e nvi e क्रिकेट के अन्यपदा एक स्वाहता के के क्षेत्र के अन्य का का वित्र के क्षेत्र के क्षेत्र का क्षेत्र के क्षेत्र के

## Example 143 - Land State Control of the Example 143 - Land State Control of the State Control

ના માના માર્ગ કે માનું કિન્સ હાઇ ભારત છે. તેના હાઇમાં પુરાસભાદી ભારત કે ફિલ્મ કરવી કરો માત્ર જાણા ધારી છે. ન

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)benzonitrile, product of example 130 d), with piperidine there was obtained: 4-(2-methyl-4-piperidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile hydrochloride as a yellow solid. ISP mass spectrum, m/e=35813 (M+1 calculated-for C23H23N-0:358); ohn-T-violomethy) bermongrife, product of example 130 35 high (5). 34 methylantinolygical file there was

# legamentmile as a placed form: ISP make upotingm, m/s; \$75.4 (M+1 calculated for first 100) forms and the background of the cample-144 of the cample of the

- Printer (S - 4. Linethy 4-7 and hydrann-printed din-1-1) quincle - relog metricle

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-15 benzonitrile, product of example 130 d), with morpholine there was obtained: 4-(2 methyl-4-morpholin-4-yl-quinolin-7-yloxymethyl)-benzonitrile hydrochloride as a light vellow solid. ISP mass spectrum, m/e: 360.3 (M+1 calculated for C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>: 360). the complex and the confession of a least of the petition of a violation of the confession of the conf

# -andi--) --- in the in 7-year mernel, being farrie by drocklande as a yellow sould Example 145 Example 145 Example 145 Example 145 Example 145

begrooting, product of example 150 dl. with peneriding their was obtained to 4-methy-

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)benzonitrile, product of example 130 d), with (R,S)=3-(diethylamino)pyrrolidine there was obtained: (R,S)-4-[4-(3-diethylamino-pytrolidin-1-yl)-2-methyl-quinolin-7yloxymethyl]-benzonitrile hydrochloride as a light brown solid. ISP mass spectrum, m/e: 415.4 (M+1 calculated for C22H21N3O2: 415). 4-c-1010-2-5101011-51. 1002n-7-vioyenes

and in this properties example lovely, with marchobase there was objected

Se tras spectrum, mer 3503 (1) + calculated for C. Ho. N.O. 360).

Example 146 In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)benzonitrile, product of example 130 d); with (R.S)-2-(pyrrolidin-3yl)-pyridine there was obtained: (R,S)-4-[2-methyl-4-(3-pyridin-2-yl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-

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benzonitrile hydrochloride as a brown solid. ISP mass spectrum, m/e: 421.4 (M+1 calculated for  $C_{27}H_{24}N_4O$ : 421).

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# Example 147 The manufactural distribution is a series to work in a sample representation of the series of the ser

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R,S)-4-(pyrrolidin-3-yl)-pyridine there was obtained: (R,S)-4-[2-methyl-4-(3-pyridin-4-yl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile as a white solid. ISP mass spectrum, m/e: 421.4 (M+1 calculated for C<sub>27</sub>H<sub>24</sub>N<sub>4</sub>O: 421).

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# calculated for Co-Halk-Or 421.

In analogy to example 130, on reaction of 4–(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d); with (S)-4–(2-pyrrolidinylmethyl)pyrrolidine there was obtained: (S)-4–[2-methyl-4-(2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile hydrochloride as a brown solid. ISP mass spectrum; m/e: 427.6 (M+1 calculated for C<sub>27</sub>H<sub>30</sub>N<sub>4</sub>©: 427).

# Example 149

phylogen a white solid. ISP mass specifying more 421.4 (MH s. curculated for

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R.S)-3-(methylsulfonyl)-pyrrolidine there was obtained: (R,S)-4-[4-(3-methanesulfonyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile hydrochloride as a light brown solid. ISP mass spectrum; in/e: 422.4 (M+1 calculated for C2H22N3O3S: 422)

Example 150

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In analogy to example 130, on reaction of 4. (4-chloro-2-methyl-quinolin-7-yloxymethyl)-benzonitrile, product of example 130 d), with (R,S)-3-methyl-piperidine there was obtained: (R,S)-4-[2-methyl-4-(3-methyl-piperidin-1-yl)-quinolin-7-yloxymethyl]-benzonitrile hydrochloride as a light yellow solid. ISP mass spectrum, m7e: 372.4 (M+1) calculated for C<sub>24</sub>H<sub>2-</sub>N<sub>3</sub>O: 372).

### Example 151

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)benzonitrile, product of example 130 d), with 1,4-dioxa-8-azaspiro{4.5}decane there was obtained: 4-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-2-methyl-quinolin-7-yloxymethyl]benzonitrile as a light yellow solid. ISP mass spectrum, m/e: 416.4 (M+1 calculated for C<sub>25</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>: 416).

In analogy to example 130, on reaction of 4-(4-chloro-2-methyl-quinolin-7-yloxymethyl)-10 benzonitrile, product of example 130 d), with (R<sub>i</sub>S)<sub>7</sub>3-(hydroxymethyl)piperidine there was obtained: (R,S)- 4-[4-(3-hydroxymethyl-piperidin-1-yl)-2-methyl-quinolin-7yloxymethyl]-benzonitrile as a light yellow solid. ISP mass spectrum, m/e: 3883 (M+T calculated for C2H25N3O2:388): 150 Ch. with 1, 1-diaga-5-agas pire 4.5 decore there was over the selection of the digraph experience of a find of the lamental outrous. The consumitation

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A compound of formula I can be used in a manner known per se as the active ingredient for the production of tablets of the following composition:

### <u>Per tablet</u>

: - analogy to evapippe 13(), pa resetion of 4 (4, chi an-2-methy) equinolis-7-violame nyl-Active ingredient act of example 130 chromosome 3-thydroxymethyl poperidine there Microcrystalline cellulose 3-hydroxymeth 155 mg risin-1-vi): 2 methyl-duhwho-7-Corn starch assessment and the state of the Tale northir conception of the state of mg-dicar bearing the filterine there was Hydroxypropylmethylcellulose 20 mg The wife wireled and analyzing are more than a four forest and the

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### Example B

A compound of formula I can be used in a manner known per se as the active ingredient for the production of capsules of the following composition:

	Per capsule	
٠.	The state of the small state in the state of	
5	Active ingredient	
	Corn starch	
	Lactose 95.0 mg	. <b>.</b>
	Talc 4.5 mg	•
:	Magnesium stearate 0.5 mg	•
10	220.0 mg	

### CLAIMS

1. Compounds of formula I

$$\begin{array}{c|c}
R \\
A \\
R^5
\end{array}$$

$$\begin{array}{c|c}
R^5 \\
A \\
N \\
R^6
\end{array}$$

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wherein

R<sup>1</sup>-is hydrogen; alkyl, alkoxyalkyl, alkenyl, alkinyl, hydroxyalkyl, aralkyl, heterocyclylalkyl, cycloalkylalkyl, NH<sub>2</sub>-SO<sub>2</sub>-, monoalkylamino-SO<sub>2</sub>-, dialkylamino-SO<sub>2</sub>-, alkyl-SO<sub>2</sub>-, aryl, NH<sub>2</sub>-alkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxycarbonylalkyl, carboxyalkyl, aryl-SO<sub>2</sub>-O-alkyl, cycloalkyl or cycloalkylalkyl;

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\_ T,

R<sup>2</sup> is hydrogen, halogen, alkyl, alkenyl, alkinyl, aralkyl, heteroarylalkyl, hydroxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkoxyalkyl, aryloxy, arylamino, heteroarylamino, NH<sub>2</sub>-, monoalkylamino, dialkylamino, heterocyclyl, arylalkylamino, heteroarylalkylamino, arylalkoxy, or heteroarylalkoxy;

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R<sup>3</sup> is hydrogen, alkyl, NH<sub>2</sub>-, monoalkylamino, dialkylamino or alkoxy;

R<sup>4</sup> is hydrogen, alkyl, cycloalkyl, alkoxy, hydroxy, NH<sub>2</sub>-, monoalkylamino, dialkylamino, acetylamino, cyano, hydroxyalkyl, alkoxyalkyl, cycloalkoxy, alkoxyalkoxy, cycloalkylalkoxy, heterocyclyl, heterocyclyloxy, heterocyclyloxyalkoxy, hydroxyalkoxy, alkoxycarbonyl, carboxy, heterocyclylalkyl, alkyl-SO<sub>2</sub>- or aryl-SO<sub>2</sub>-;

and the state of t

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R<sup>5</sup> is hydrogen, alkyl, cycloalkyl, alkoxy, hydroxy NH<sub>2</sub>-, monoalkylamino, dialkylamino, acetylamino, cyano, hydroxyalkyl, alkoxyalkyl, cycloalkoxy, alkoxyalkoxy, cycloalkylalkoxy, heterocyclyl, heterocyclyloxy,

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heterocyclyloxyalkoxy, hydroxyalkoxy, alkoxycarbonyl, carboxy, heterocyclylalkyl, alkyl-SO<sub>2</sub>- or aryl-SO<sub>2</sub>-;

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A is a 5- to 10- membered mono- or bicyclic saturated heterocyclic ring comprising the nitrogen atom which is attached to the quinoline ring and optionally one or two further heteroatoms which are independently selected from oxygen, sulfur and nitrogen;

and pharmaceutically acceptable salts and esters thereof.

- 2. Compounds according to claim 1, wherein
- R<sup>1</sup> is hydrogen, alkyl, alkoxyalkyl, alkenyl, alkinyl, hydroxyalkyl, aralkyl,

  heterocyclyialkyl, cycloalkylalkyl, NH<sub>2</sub>-SO<sub>2</sub>-, monoalkylamino-SO<sub>2</sub>-,

  dialkylamino-SO<sub>2</sub>- or alkyl-SO<sub>2</sub>-;
  - R<sup>4</sup> is hydrogen, alkyl, alkoxy, hydroxy, NFI<sub>2</sub>-, monoalkylamino, dialkylamino, acetylamino of cyano; have have a thick are independently selected R<sup>5</sup> is hydrogen; and the selected R<sup>5</sup> is
- 15 quinoline ring and a -(CH<sub>2</sub>)<sub>n</sub>-moiety with n being 4, 5, or 6.
  - 3. Compounds according to claims 1 or 2; wherein R<sup>1</sup> is hydrogen, cycloalkylalkyl, aralkyl, or heteroarylalkyl, action with the second state of t
- 4. Compounds according to any one of claims 1 to 3, wherein R<sup>1</sup> is hydrogen, aralkyl or heteroarylalkyl.
  - 5. Compounds according to any one of claims 1 to 4; wherein R<sup>1</sup> is hydrogen, phenylalkyl or pyridinylalkyl, wherein the phenyl- and the pyridinyl cycles are optionally substituted with one to three substituents independently selected from alkoxy, cyano and halogen.
- 25 6. Compounds according to any one of claims 1 to 5, wherein R<sup>d</sup> is hydrogen, cyclopropylmethyl. (methoxyphenyl)methyl, (cyanophenyl)methyl, (chlorophenyl)methyl, pyridinylmethyl, chloropyridinylmethyl fluoropyridinylmethyl

- 7. Compounds according to any one of claims I to 6, wherein R<sup>2</sup> is hydrogen, alkyl or halogen.
- 8. Compounds according to claim 7, wherein R<sup>2</sup> is hydrogen.
- 9. Compounds according to claim 7, wherein R<sup>2</sup> is alkyl.
- 5 10. Compounds according to claim 7, wherein R is hydrogen, butyl, fluoro, chloro or bromo.
  - 11. Compounds according to any one of claims 1 to 10, wherein R<sup>3</sup> is hydrogen, alkyl, or NH<sub>2</sub>.
  - 12. Compounds according to claim 11 wherein Rais alkylerant is in an agent a color
- 10 13. Compounds according to claim 12, wherein R<sup>3</sup> is methyl.
  - 14. Compounds according to any one of claims 1 to 13, wherein R<sup>4</sup> is hydrogen, alkoxy, alkoxyalkyl, hydroxyalkyl or hydroxyaltyl alkoxy.
  - 15. Compounds according to claim 14, wherein Riss hydrogen hand, hupro, chiero cr
- 16. Compounds according to any one of claims 1 to 15, wherein A is a pyrrolidinyl or azepanyl ring.
  - 17. Compounds according to claim 16, wherein A is a pyrrolidinyl ring.
  - 18. Compounds according to any one of claims 1 to 17, wherein R is hydrogen.
  - 19. Compounds according to claim 17, wherein R is methyl

    19. Compounds according to any one of claims 1 to 18 selected from the control of t
- - 2-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
  - 4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
  - 7-(5-chloro-benzyloxy) 2-methyl-4-pyrrolidin-1-yl-quinoline; 1118
  - 7-(4-chloro-benzyloxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;

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**:**{:

	-	(S)-4-[4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-
		benzonitrile;
:	•	6-butyl-4-pyrrolidin-1-yl-quinolin-7-ol;
_''i		4-(6-butyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
5		4-azepan-1-yl-2-methyl-7-(pyridin-4-ylmethoxy)-quinoline;
•		4-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile;
:		3-(4-azepan-1-yl-2-methyl-quinolin-7-yloxymethyl)-benzonitrile;
	***	2-Varateban-1-At-a month Mannatas Assault and Science
		7-(2-chloro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
		(S) 4-(3-ethoxy-pyrrolidin-1-yl)-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-
10	;	quinoline; n-bitty = pyt, midit - all guerten - col; n-bitty = pyt, midit - all guerten - col;
, Tr		(S) 7-(2-chloro-pyridin-3-ylmethoxy)-4-(3-ethoxy-pyrrolidin-1-yl)-2-methyl-quinoline;
ñ		2-2751 and vi-2, metryl-7-(pyridin-4-vi/nethox, -Ciriachies (S)-7-(2-chloro-pyridin-3-ylmethoxy)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-
٠		methyl-quinoline; nathyl-quinotin-7-vioryawittyii-bergoeneits.
15		(S)-7=(2-fluoro-pyridin-3-ylmethoxy)-4-(2-methoxymethyl-pyrrolidin-1-yl)-2-
		methyl-quinoline;
		(S)- [1-[7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-quinolin-4-yl]-pyrrolidin-2-
•		yl}-methanol;
111	•	200 (1) Francisco de la companya del companya de la companya del companya de la companya del companya de la companya de la companya de la companya del companya de la companya del companya de la companya de la companya de la companya de la companya del companya de la companya
20		yl)-methanol;
:		4-(6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinolin-7-yloxymethyl)-benzonitrile;
		6-fluoro-7-(2-fluoro-pyridin-3-ylmethoxy)-2-methyl-4-pyrrolidin-1-yl-quinoline;
15.	:	7-(2-chloro-pyridin-3-ylmethoxy)-6-fluoro-2-methyl-4-pyrrolidin-1-yl-quinoline
		(S)= 4-[4-(3-methoxy-pyrrolidin-1-yl)-2-methyl-guinolin-7-yloxymethyl]-
25		benzonitrile;-

erostaries (\* 2

- (S)-4-[6-fluoro-4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
- (S)-4-[4-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile;
- (R)-4-[4-(3-hydroxy-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]benzonitrile;
  - (S)-4-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]-benzonitrile and
- (R)-4-[4-(2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-quinolin-7-yloxymethyl]
  10 benzontrile.
  - 20. A process for the preparation of a compound according to any one of claims 1 to 19 comprising one of the following reactions
    - a) reaction of a compound of the formula Ia in the presence of a compound of the formula R-Hall

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entrokes for the restaurable of seame and activities forther one of claims I to 19 in the first of the first

wherein R1, R2, R3, R4, R5 and A are as defined in claim I and Hal is halogen; or

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b) a Pd catalyzed C/O, C/N or C/C bond forming reaction of a compound of formula Ic in order to obtain a compound of formula Ic

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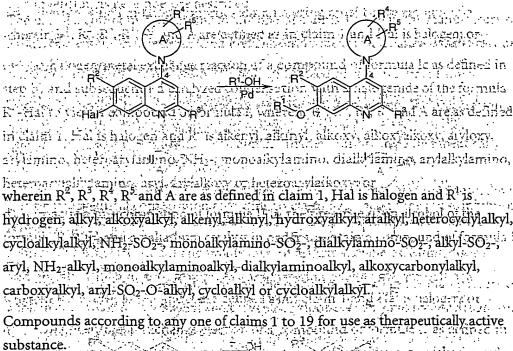
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and A are defined as in claim 1 and Hal is halogen; or

- c) a halogen/metal exchange reaction of a compound of formula Ic as defined in step b) and subsequent Pd catalyzed condensation with a halogenide of the formula R2-Hall to yield a compound of formula I, wherein R1, R3, R4, R5 and A are as defined in claim I, Hal is halogen and R2 is alkenyl, alkinyl, alkoxy, alkoxyalkoxy, aryloxy, arylamino, heteroarylamino, NH2-, monoalkylamino, dialkylamino, arylalkylamino, heteroarylalkylamino, aryl, arylalkoxy or heteroarylalkoxy; or
- reaction of a compound of formula II in the presence of an alcohol of the formula R<sup>1</sup>-OH and a palladium catalyst in order to obtain a compound of formula I



- Compounds according to any one of claims 1 to 19 for use as therapeutically active 21. substance.
- Compounds according to any one of claims 1 to 19 for the preparation of 22. medicaments for the prophylaxis and therapy of illnesses which are caused by 20 disorders associated with the NPY receptor kriamino, dialetterings, crylalsylanuao,

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- 23. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 19 and a therapeutically inert carrier.
- 24. The use of a compound according to any one of claims 1 to 19 for the preparation of medicaments for the treatment and prophylaxis of arthritis, diabetes, eating disorders and obesity.
- 25. A compound according to any one of claims 1 to 19, when manufactured according to a process of claim 20.
- 26. A method for the treatment and prophylaxis of arthritis, diabetes, eating disorders and obesity; which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 19
  - 27. A method of treatment of obesity in a human in need of such treatment which
  - comprises administration to the human a therapeutically effective amount of a compound as defined in any one of the claims 1 to 19 and a therapeutically effective amount of a lipase inhibitor.
- 15 28. The method according to claim 27, wherein the lipase inhibitor is orlistat.
  - 29. The method according to any one of claims 27 or 28 for simultaneous, separate or sequential administration.
- 30. The use of a compound according to any one of claims 1 to 19 in the manufacture of a medicament for the treatment and prevention of obesity in a patient who is also a receiving treatment with a lipase inhibitor.
  - 31. The use according to claim 30, wherein the lipase inhibitor is offistate of the lipase inhibitor is of the lipase inhibitor in lipase inhibitor is offistate of the lipase inhibitor is offistate of the lipase inhibitor is offistat
  - 32. The pharmaceutical composition of claim 23 further comprising a therapeutically effective amount of a lipase inhibitor.
  - 33. The pharmaceutical composition according to claim 32, wherein the lipase inhibitor is or list of the control of the contro
    - 34. The invention as hereinbefore described.

### ERNATIONAL SEARCH REPORT

Inconational Application No PCT/EP 02/05120

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 CO7D215/42 CO7E CO7D401/04 C07D401/12 C07D405/12 CO7D409/12 A61K31/4706 A61K31/4709 A61P3/04 A61P19/02 A61P3/10 CO7D401/14 CO7D405/14 C07D491/10 According to International Patent Classification (IPC) or to both national classification and IPC Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data C. DOCUMENTS CONSIDERED TO BE RELEVANT Category ° Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. X US 4 035 367 A (SIMPSON WILLIAM R) 1-19. 12 July 1977 (1977-07-12) 21-26 column 1, line 23 -column 2, line 55 column 4, line 4 -column 5, line 5; examples 4G,4H,Z-33,Z-34 Further documents are listed in the continuation of box C. Х Patent family members are listed in annex. Special categories of cited documents: 'T' later document published after the international filing date or priority date and not in conflict with the application but clied to understand the principle or theory underlying the invasion. 'A' document defining the general state of the art which is not considered to be of particular relevance 'E' earlier document but published on or after the international filing date "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken atone document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "Y" document of particular relevance; the claimed invention cannot be considered to involve an-inventive step when the document is combined with one or more other such docu-ments, such combination being obvious to a person skilled in the art. document referring to an oral disclosure, use, exhibition or document published prior to the international filing date but tater than the priority date claimed \*&\* document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 7 August 2002 02/09/2002 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340–2040, Tx. 31 651 epo nl, Fax: (+31-70) 340–3016 Seymour, L

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International Application No
PCT/EP 02/05120

C/Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	FC1/EF 02/03120		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X .	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; CRONIN, TIMOTHY H.; HESS, HANS J. E.: "Hypotensive and bronchodilatory quinolines, isoquinolines, and quinazolines" Database accession no. 70:68419 (DN) XP002209016 RN 21560-24-7, 21560-25-8, 21579-67-9 abstract & ZA 6 706 512 A (PFIZER, CHAS., AND CO., INC.) 3 June 1968 (1968-06-03)	1-19, 21-23,25		
χ	US 3 272 824 A (FREDERICK EBETINO FRANK ET AL) 13 September 1966 (1966-09-13) column 1, line 39 - line 54; claim 1; examples VII,XIII	1-19, 21-23,25		
X	GB 991 838 A (RHONE POULENC SA) 12 May 1965 (1965-05-12) page 4, line 45 - line 49; claims 1,10,11,26; examples V,XX,XXI	1-19,21, 23,25		
X	GAUTHIER B ET AL: "RECHERCHE SUR LES AMINOQUINOLEINES. ETUDES CHIMIQUE, ANTIPARASITAIRE, ANTIMICROBIENNE ET ANTIFONGIQUE DE (MONO, DI ET TRICHLORACETYL-4 PIPERAZINYL-1)-4 QUINOLEINES//AMINOQUINOLEIN RESEARCH. CHEMICAL, ANTIPARASITIC, ANTIMICROBIAL AND ANTIFUNGAL STUDY OF (" ANNALES PHARMACEUTIQUES FRANCAISES, MASSON, PARIS, FR, vol. 1, no. 44, 22 August 1986 (1986-08-22), pages 55-64, XP001063055 ISSN: 0003-4509 scheme 1 abstract; tables I-III	1-19,21, 23,25		
Х	EP 0 882 717 A (KYOWA HAKKO KOGYO KK) 9 December 1998 (1998-12-09) page 9, formula II example 407	1-19		
P, X	WO 02 20488 A (HOFFMANN LA ROCHE) 14 March 2002 (2002-03-14) page 8, line 9 - line 10 claims	1-33		

. International application No. PCT/EP 02/05120

### INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)	
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:	
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:	
Although claims 26-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.	
2. X Claims Nos.: 34 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:	
see FURTHER INFORMATION sheet PCT/ISA/210	
·	
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).	
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)	
This International Searching Authority found multiple inventions in this international application, as follows:	
1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable daims.	
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.	
· 	
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:	
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:	
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Remark on Protest  The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.	

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 34

The present claims do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The functional term "pharmaceutically acceptable esters" (including "physiologically acceptable equivalents" thereof; cf. present description, p. 7, lines 16-23) does not enable the skilled person to determine which technical features are necessary to perform the stated function. It is thus unclear which specific compounds fall within its scope. A lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search does not include "pharmaceutically acceptable esters" of the compounds of formula I.

The vague reference in claim 34 to "the invention as hereinbefore described" leaves the reader in doubt as to the scope of said claim (Article 6 PCT). The resulting lack of clarity is such as to preclude a meaningful search of this claim.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

### ERNATIONAL SEARCH REPORT

Information on patent family members

PCT/EP 02/05120

			101/21 02/05120			
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ZA 6706512	Α		NONE			<del>^</del>
US 3272824	———— А	13-09-1966	BE	640817	 A	01-04-1964
			CH	439290 A		15-07-1967
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Form PCT/ISA/210 (patent family annex) (July 1992)